



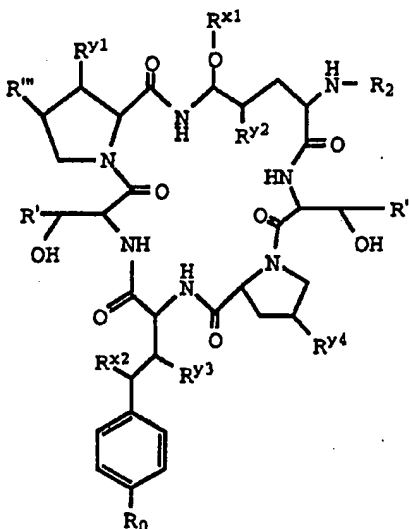
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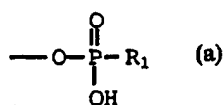
(54) Title: CYCLIC PEPTIDE ANTIFUNGAL AGENTS

(57) Abstract

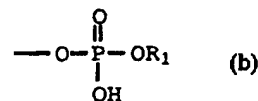
Provided are pharmaceutical formulations, and methods of inhibiting fungal and parasitic activity using a compound of formula (I), wherein R' is hydrogen, methyl or -CH₂C(=O)NH₂; R'' and R''' are independently hydrogen or methyl; R^{x1} is C₁-C₆ alkyl, benzyl, -(CH₂)₂Si(CH₃)₃, -CH₂CH=CH₂, -CH₂CHOHCH₂OH, -(CH₂)₆COOH, -(CH₂)₆NR^{z1}R^{z2}, -(CH₂)₆POR^{z3}R^{z4} or -[(CH₂)₂O]₄-(C₁-C₆)alkyl; a, b and c are independently 1, 2, 3, 4, 5 or 6; R^{z1} and R^{z2} are independently hydrogen, C₁-C₆ alkyl, or R^{z1} and R^{z2} combine to form -CH₂(CH₂)₆CH₂-; R^{z3} and R^{z4} are independently hydroxy, or C₁-C₆ alkoxy; d is 1 or 2; e is 1, 2 or 3; R^{x2}, R^{y1}, R^{y2}, R^{y3} and R^{y4} are independently hydroxy or hydrogen; R₀ is hydroxy, -OP(=O)(OH)₂ or a group of formulae (a) or (b); R₁ is C₁-C₆ alkyl, phenyl, p-halo-phenyl, p-nitrophenyl, benzyl, p-halo-benzyl or p-nitro-benzyl; and R₂ is an acyl side chain as defined herein.



(I)



(a)



(b)

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CYCLIC PEPTIDE ANTIFUNGAL AGENTS

This invention relates to semi-synthetic cyclic peptide compounds which are useful as antifungal and antiparasitic agents and which have improved stability and water solubility. In particular, it relates to derivatives of the echinocandin class of cyclic peptides; to methods for treating fungal and parasitic infections, and to formulations useful in the methods.

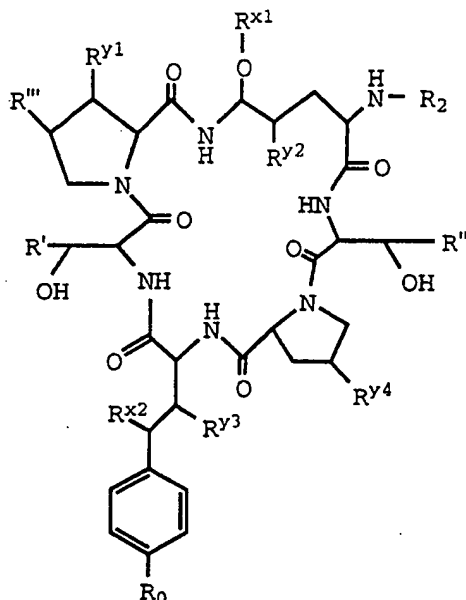
The compounds provided by this invention are semi-synthetic compounds derived from cyclic peptides which are produced by culturing various microorganisms. A number of cyclic peptides are known in the art including echinocandin B (A30912A), aculeacin, mulundocandin, sporiofungin and S31794/F1.

In general, these cyclic peptides may be structurally characterized as a cyclic hexapeptide core (or nucleus) with an acylated amino group on one of the core amino acids. The amino group is typically acylated with a fatty acid group forming a side chain off the nucleus. For example, echinocandin B has a linoleoyl side chain while aculeacin has a palmitoyl side chain.

The fatty acid side chains may be removed from the cyclic peptide core to provide an amino nucleus (for example, a compound of formula I, below, where R_2 is hydrogen). The amino group may then be re-acylated to provide semi-synthetic compounds such as those claimed in the present application.

The echinocandin B nucleus has been re-acylated with certain non-naturally occurring side chain moieties to provide a number of antifungal agents (see, Debono, U.S. Pat. Ser. No. 4,293,489). Among such antifungal agents is cilofungin which is represented by a compound of formula I where R' , R'' and R''' are methyl; R^{x1} is hydrogen, R^{x2} , RY^1 , RY^2 , RY^3 , RY^4 and R_0 is hydroxy and R_2 is p-(octyloxy)benzoyl.

The present invention provides a compound of formula I:



5 wherein:

R' is hydrogen, methyl or $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$;

R'' and R''' are independently hydrogen or methyl;

RX1 is C_1 - C_6 alkyl, benzyl, $-(\text{CH}_2)_2\text{Si}(\text{CH}_3)_3$,
 $-\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CHOHCH}_2\text{OH}$, $-(\text{CH}_2)_a\text{COOH}$, $-(\text{CH}_2)_b\text{NR}^{z1}\text{R}^{z2}$,
 10 $-(\text{CH}_2)_c\text{POR}^{z3}\text{R}^{z4}$ or $-[(\text{CH}_2)_2\text{O}]_d-(\text{C}_1-\text{C}_6)\text{alkyl}$;

a, b and c are independently 1, 2, 3, 4, 5 or 6;

R^{z1} and R^{z2} are independently hydrogen, C_1 - C_6 alkyl,
 or R^{z1} and R^{z2} combine to form $-\text{CH}_2(\text{CH}_2)_e\text{CH}_2-$;

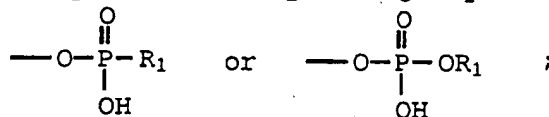
R^{z3} and R^{z4} are independently hydroxy, or C_1 - C_6
 15 alkoxy;

d is 1 or 2;

e is 1, 2 or 3;

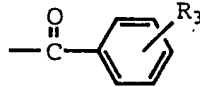
RX2, RY1, RY2, RY3 and RY4 are independently hydroxy or
 hydrogen;

20 R0 is hydroxy, $-\text{OP}(\text{O})(\text{OH})_2$ or a group of the formulae:



R_1 is C_1 - C_6 alkyl, phenyl, p-halo-phenyl, p-nitrophenyl, benzyl, p-halo-benzyl or p-nitro-benzyl;

I) R_2 is a group of the formula



where:

A) R_3 is C_1 - C_{12} alkyl, C_1 - C_6 alkoxy or quinolyl;

B) R_3 is $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$;

m and n are independently 2, 3 or 4;

p is 0 or 1; or

C) R_3 is $-Y-(C_1-C_{12} \text{ alkyl})$;

Y is $-C\equiv C-$ or $-CH=CH-$; or

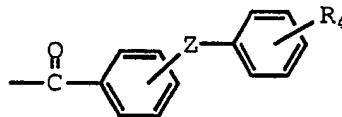
D) R_3 is $-O-(CH_2)_q-G$;

q is 2, 3 or 4;

G is C_7 - C_{10} bicycloalkyl or C_7 - C_{14}

tricycloalkyl; or

II) R_2 is a group of the formula



where:

Z is $-O-$, $-C\equiv C-$, $-CH=CH-$, $-CH_2-CH_2-$, $-CH_2-$, or a bond;

A) R_4 is hydrogen, C_1 - C_{12} alkyl, C_1 - C_{12} substituted alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} substituted alkenyl, C_2 - C_{12} alkynyl, C_2 - C_{12} substituted alkynyl, C_1 - C_{12} alkoxy, C_3 - C_{12} cycloalkyl, C_7 - C_{10} bicycloalkyl, C_7 - C_{14} tricycloalkyl, C_3 - C_{12} cycloalkoxy, naphthyl, pyridyl, thienyl, benzothienyl, quinolyl or phenyl; or

B) R_4 is phenyl substituted by amino, C_1 - C_{12} alkylthio, halo, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, C_1 - C_{12} substituted alkyl, C_2 - C_{12} substituted alkenyl, C_2 - C_{12} substituted alkynyl, C_1 - C_{12} alkoxy,

trifluoromethyl, phenyl, substituted phenyl, or phenyl substituted with a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m, n and p are as defined above; or

5

C) R_4 is C_1-C_{12} alkoxy substituted with halo, C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, C_1-C_6 alkoxy, C_2-C_{12} alkynyl, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, formamido, C_2-C_{12} alkanoylamino, or phenyl substituted with a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m, n and p are as defined above; or

10

D) R_4 is $-O-(CH_2)_r-W-R_5$;

15

r is 2, 3 or 4;

W is pyrrolidino, piperidino or piperazino;

R_5 is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl; or

20

E) R_4 is $-Y^1-R_6$;

Y^1 is $-C\equiv C-$ or $-CH=CH-$;

R_6 is C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, C_3-C_{12} cycloalkenyl, naphthyl, benzothiazolyl, thienyl, indanyl, fluorenyl, or phenyl substituted with C_1-C_{12} alkylthio, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, halo(C_1-C_6 alkoxy) or a group of the formula $-O-(CH_2)_r-W-R_5$ where r , W and R_5 are as defined above; or

25

R_6 is phenyl substituted with a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m, n and p are as defined above; or

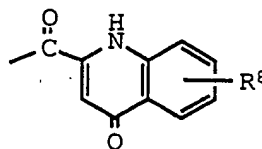
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F) R_4 is C_1-C_{12} alkoxy substituted with a group of the formula $-NHC(O)R_7$;

R_7 is C_1-C_6 alkoxy, or phenyl(C_1-C_6 alkoxy); or

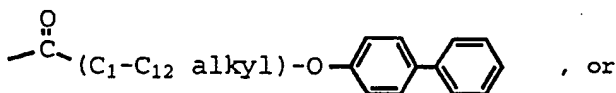
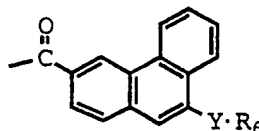
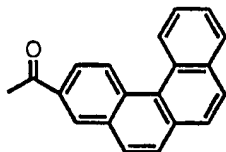
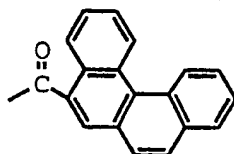
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III) R_2 is a group of the formula

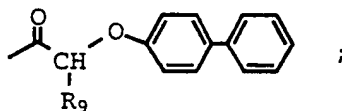


where R^8 is C_1 - C_{12} alkoxy or a group of the formula
 5 $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m , n and p are as defined above; or

IV) R_2 is a group of the formula



, or



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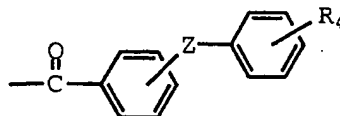
where:

Y and R_6 are as defined above;

R_9 is phenyl, C_1 - C_{12} alkyl, or C_1 - C_{12} alkoxy; or

15 V) R_2 is naphthoyl substituted with R_4 where R_4 is as defined above;
 with the provisos that

i) when R' is $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$; and $\text{R}^{\text{x}1}$ is methyl or benzyl; then R_2 is not a group of the formula



5 where:

Z is a bond;

A) R_4 is $\text{C}_1\text{-C}_{12}$ alkoxy; or

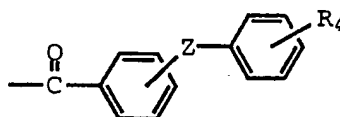
B) R_4 is phenyl substituted by $\text{C}_1\text{-C}_{12}$ alkoxy; or

10 C) R_4 is $\text{C}_1\text{-C}_{12}$ alkoxy substituted with $\text{C}_1\text{-C}_4$ alkylamino, di($\text{C}_1\text{-C}_4$ alkyl)amino; or

D) R_4 is $-\text{O}-(\text{CH}_2)_r\text{-W-R}_5$;

W is piperidino or piperazino;

15 ii) when $\text{R}^{\text{x}1}$ is $-(\text{CH}_2)_b\text{NR}^{\text{z}1}\text{R}^{\text{z}2}$; then R_2 is not a group of the formula



where:

Z is a bond;

20 A) R_4 is $\text{C}_1\text{-C}_{12}$ alkoxy; or

B) R_4 is phenyl substituted by $\text{C}_1\text{-C}_{12}$ alkoxy; or

C) R_4 is $\text{C}_1\text{-C}_{12}$ alkoxy substituted with $\text{C}_1\text{-C}_4$ alkylamino, di($\text{C}_1\text{-C}_4$ alkyl)amino; or

D) R_4 is $-\text{O}-(\text{CH}_2)_r\text{-W-R}_5$;

25 W is piperidino or piperazino;

or a pharmaceutically acceptable salt thereof.

Also provided are pharmaceutical formulations, methods for inhibiting parasitic or fungal activity and methods of treating fungal or parasitic infections which employ the compounds of the invention.

30

As used herein, the term "C₁-C₁₂ alkyl" refers to a straight or branched alkyl chain having from one to twelve carbon atoms. Typical C₁-C₁₂ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, 5-methylpentyl, hexyl, heptyl, 3,3-dimethylheptyl, octyl, 2-methyl-octyl, nonyl, decyl, undecyl, dodecyl and the like. The term "C₁-C₁₂ alkyl" includes within its definition the terms "C₁-C₆ alkyl" and C₁-C₄ alkyl."

10 The term "halo" refers to chloro, fluoro, bromo or iodo.

 The term "C₂-C₁₂ alkenyl" refers to a straight or branched alkenyl chain having from two to twelve carbon atoms. Typical C₂-C₁₂ alkenyl groups include ethenyl, 1-propen-2-yl, 3-buten-1-yl, 1-buten-2-yl, 1-buten-1-yl, 1-penten-3-yl, 2-hexen-3-yl, 1-decen-2-yl, 2-decen-5-yl and the like.

 The term "C₂-C₁₂ alkynyl" refers to a straight or branched alkynyl chain having from two to twelve carbon atoms. Typical C₂-C₁₂ alkynyl groups include ethynyl, 1-propyn-1-yl, 1-propyn-2-yl, 1-butyne-1-yl, 1-butyne-3-yl, 1-pentyne-3-yl, 4-pentyne-2-yl, 1-hexyn-3-yl, 3-hexyn-1-yl, 5-methyl-3-hexyn-1-yl, 5-octyn-1-yl, 7-octyn-1-yl, 4-decyn-1-yl, 6-decyn-1-yl and the like.

25 The term "C₁-C₁₂ alkylthio" refers to a straight or branched alkyl chain having from one to twelve carbon atoms attached to a sulfur atom. Typical C₁-C₁₂ alkylthio groups include methylthio, ethylthio, propylthio, isopropylthio, butylthio, 3-methyl-heptylthio, octylthio, 5,5-dimethyl-hexylthio and the like.

30 The term "C₁-C₁₂ alkoxy" refers to a straight or branched alkyl chain having from one to twelve carbon atoms attached to an oxygen atom. Typical C₁-C₁₂ alkoxy groups include methoxy, ethoxy, propoxy, butoxy, sec-butoxy, 35 pentoxy, 5-methyl-hexoxy, heptoxy, octyloxy, decyloxy, dodecyloxy and the like. The term "C₁-C₁₂ alkyl" includes

within its definition the terms "C₁-C₆ alkoxy" and C₁-C₄ alkoxy."

5 The terms "C₁-C₁₂ substituted alkyl," "C₂-C₁₂ substituted alkenyl" and "C₂-C₁₂ substituted alkynyl," refers to the specified moiety substituted with 1 or 2 substituents independently selected from halo, hydroxy, protected hydroxy, amino, protected amino, C₁-C₇ acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carbamoyloxy, cyano, methylsulfonylamino, phenyl, substituted phenyl or
10 C₁-C₁₂ alkoxy.

The term "substituted phenyl" refers to a phenyl group substituted with 1, 2 or 3 substituents independently selected from halo, hydroxy, protected hydroxy, cyano, nitro, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy, carboxy, protected
15 carboxy, carboxymethyl, hydroxymethyl, amino, aminomethyl trifluoromethyl or N-methylsulfonylamino.

The term "C₃-C₁₂ cycloalkyl" refers a saturated hydrocarbon ring structure having from three to twelve carbon atoms. Typical C₃-C₁₂ cycloalkyl groups include
20 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, cyclooctyl and the like.

The term "C₃-C₁₂ cycloalkoxy" refers to a C₃-C₁₂ cycloalkyl group attached to an oxygen atom. Typical C₃-C₁₂ cycloalkoxy groups include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and
25 cycloheptyloxy and the like.

The term "C₃-C₁₂ cycloalkenyl" refers to a hydrocarbon ring structure having from three to twelve carbon atoms with at least one double bond. Typical C₃-C₁₂ cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl and the like.
30

The term "methyl(C₃-C₁₂ cycloalkyl)" refers to a C₃-C₁₂ cycloalkyl group that is substituted with a methyl group. Typical methyl(C₃-C₁₂ cycloalkyl) groups include
35 2-methylcyclopropyl, 2-methylcyclobutyl, 3-methylcyclopentyl, 4-methylcyclohexyl and the like.

The term "C₁-C₄ alkylamino" refers to a straight or branched alkylamino chain having from one to four carbon atoms attached to a nitrogen atom. Typical C₁-C₄ alkylamino groups include methylamino, ethylamino, propylamino, isopropylamino, butylamino, *sec*-butylamino and the like.

The term "di(C₁-C₄ alkyl)amino" refers to a di(C₁-C₄ alkyl)amino chain having two straight or branched alkyl chains of from one to four carbon atoms attached to a common nitrogen atom. Typical di(C₁-C₄ alkyl)amino groups include dimethylamino, diethylamino, ethylmethylamino, methylisopropyl-amino, dipropylamino, dibutylamino, methylbutylamino, *t*-butylisopropylamino, di-*t*-butylamino and the like.

The term "C₂-C₁₂ alkanoyl" represents a straight or branched chain alkyl chain having from one to four carbon atoms attached to a carbonyl moiety. Typical C₂-C₁₂ alkanoyl groups include ethanoyl, propanoyl, isopropanoyl, butanoyl, isobutanoyl, *sec*-butanoyl, *t*-butanoyl, pentanoyl and the like.

The term "C₂-C₁₂ alkanoylamino" represents a straight or branched chain alkyl group attached to a carbonylamino moiety. Typical C₂-C₁₂ alkanoylamino groups include ethanoylamino, propanoylamino, isopropanoylamino, butanoyl-amino, isobutanoylamino, *sec*-butanoylamino, *t*-butanoylamino, pentanoylamino and the like.

The terms "C₇-C₁₀ bicycloalkyl" represents two fused cycloalkyl rings having a total of seven to ten carbon atoms and "C₇-C₁₄ tricycloalkyl" represents three fused cycloalkyl rings having a total of seven to fourteen carbon atoms. Typical "C₇-C₁₀ bicycloalkyl" and "C₇-C₁₄ tricycloalkyl" groups include bicyclo[2.2.1.]hept-2-yl, bicyclo[2.2.1.]hept-4-en-2-yl, bicyclo[3.3.1.]non-3-yl, bicyclo[3.3.1.]non-2-yl, bicyclo[3.2.1.]oct-2-yl, bicyclo[2.2.2.]oct-2-yl, bicyclo[2.2.2.]oct-5-en-2-yl, adamantyl and the like.

The term "amino-protecting group" as used in the specification refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino-protecting groups include formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl groups, or urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, *t*-butoxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl and the like; benzoylmethylsulfonyl, 2-nitrophenylsulfenyl, diphenylphosphine oxide and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule including

any other amino-protecting group(s). Preferred amino-protecting groups are *t*-butoxycarbonyl (*t*-Boc), allyloxycarbonyl and benzyloxycarbonyl (CbZ). Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapter 2, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and sons, New York, N.Y., 1981, Chapter 7.

The term "inhibiting", i.e. a method of inhibiting parasitic or fungal activity, includes stopping, retarding or prophylactically hindering or preventing the growth or any attending characteristics and results from the existence of a parasite or fungus.

The term "contacting", i.e. contacting a compound of the invention with a parasite or fungus, includes a union or junction, or apparent touching or mutual tangency of a compound of the invention with a parasite or fungus. However, the term does not imply any further limitations to the process, such as by mechanism of inhibition, and the methods are defined to encompass the spirit of the invention, which is to inhibit parasitic and fungal activity by the action of the compounds and their inherent antiparasitic and antifungal properties, or in other words, the compounds, used in the claimed methods are the causative agent for such inhibition.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid,

phosphoric acid and the like, and organic acids such as *p*-toluenesulfonic, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

5 Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate,
10 formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate,
15 xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, γ -hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically
20 acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

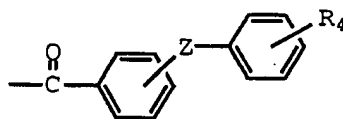
Base addition salts include those derived from
25 inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium
hydroxide, ammonium hydroxide, potassium carbonate, sodium
30 carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular
counterion forming a part of any salt of this invention is
35 not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion

does not contribute undesired qualities to the salt as a whole.

Typical examples of acyl groups at R_2 in formula I include benzoyl substituted by a polyoxa-alkyl group such as 2-methoxyethoxy (p is 0, m is 1), 2-ethoxyethoxy (p is 0, m is 2), 2-(2-ethoxyethoxy)ethoxy (m is 2, p is 1, n is 2), 3-(2-ethoxyethoxy)propoxy, 4-(2-methoxyethoxy)butoxy, and the like, or benzoyl substituted by alkynyl groups ($-C\equiv C-(C_1-C_{12} \text{ alkyl})$) such as propynyl, butynyl, hexynyl, undecynyl, and the like, or *cis* or *trans* alkenyl groups ($-CH_2=CH_2-(C_1-C_{12} \text{ alkyl})$) such as propenyl, butenyl, hexenyl, decenyl and the like.

Examples of acyl groups where R_2 is a group of the formula



include diphenyl ethers (Z is $-O-$), diphenyl acetylenes (Z is $-C\equiv C-$), stilbenes (Z is $-CH=CH-$) and biphenyls (Z is a bond).

Examples of diphenyl ether groups include 4-(4-butoxyphenoxy)benzoyl, 4-(4-hexoxyphenoxy)benzoyl, 4-(4-ethoxyphenoxy)benzoyl, 4-(4-phenyloxyphenoxy)benzoyl, 4-[4-(4-dodecyloxyphenoxy)benzoyl, 4-[4-(3-dimethylaminopropoxy)phenoxy]benzoyl and the like.

Examples of diphenyl acetylene and stilbene groups include 4-styrylbenzoyl, 4-(4-methoxystyryl)benzoyl, 4-(4-butoxystyryl)benzoyl, 4-(phenylethynyl)benzoyl, 4-(4-ethoxyphenylethynyl)benzoyl, 4-(4-cyclohexyloxyphenylethynyl)benzoyl and the like.

Examples of biphenyl groups include 4-[4-(butoxy)phenyl]benzoyl, 4-[4-(cyclobutylmethoxy)phenyl]benzoyl, 4-[4-(cyclopentylmethoxy)phenyl]benzoyl, 4-[4-(cyclohexylethoxy)phenyl]benzoyl, 4-[4-(hexoxy)phenyl]benzoyl, 4-phenylbenzoyl, 4-[4-(11-amino-undecyloxy)phenyl]benzoyl, 4-[4-(11-formamidoundecyloxy)phenyl]benzoyl, 4-[4-(iso-pentoxy)phenyl]benzoyl and the like.

Examples of biphenyl groups where R_4 is
-O-(CH₂)_r-W-R₅ include 4-[4-[2-(N-cyclohexylpiperidino-4-
yl)ethoxy]phenyl]benzoyl, 4-[4-[2-(N-hexylpiperidino-4-
yl)ethoxy]phenyl]benzoyl, 4-[4-[2-(4-benzylpiperidino)-
ethoxy]phenyl]benzoyl, 4-[4-[2-(4-cyclohexylpiperidino)-
ethoxy]phenyl]benzoyl and the like.

Examples of biphenyl and diphenyl ether groups
where R_4 is -Y¹-R₆ include 4-[4-(phenylethynyl)phenyl]
benzoyl, 4-[4-(phenylethynyl)phenoxy]benzoyl, 4-[4-
(hexynyl)phenyl]benzoyl, 4-[4-(styryl)phenoxy]benzoyl, 4-
[4-[4-(4-methylpiperidino)ethoxy]phenylethynyl]phenyl]
benzoyl, and the like.

Acyl groups where R_4 is -O-(CH₂)_r-W-R₅ may form
acid addition salts of the basic amino groups of the
piperidine and piperazine heterocyclic groups with organic
or mineral acids such as hydrochloric acid, hydrobromic
acid, sulfuric acid and phosphoric acid and with organic
acids such as the sulfonic acids, benzenesulfonic acid,
toluenesulfonic acid, methanesulfonic acid, acetic acid,
chloroacetic acid, trifluoroacetic acid, benzoic acid,
isophthalic acid, salicylic acid, citric acid, malic acid,
succinic acid, malonic acid and the like.

Table 1, below, provides further examples of
acyl groups, R_2 , found on cyclic peptides of formula I.

Table 1

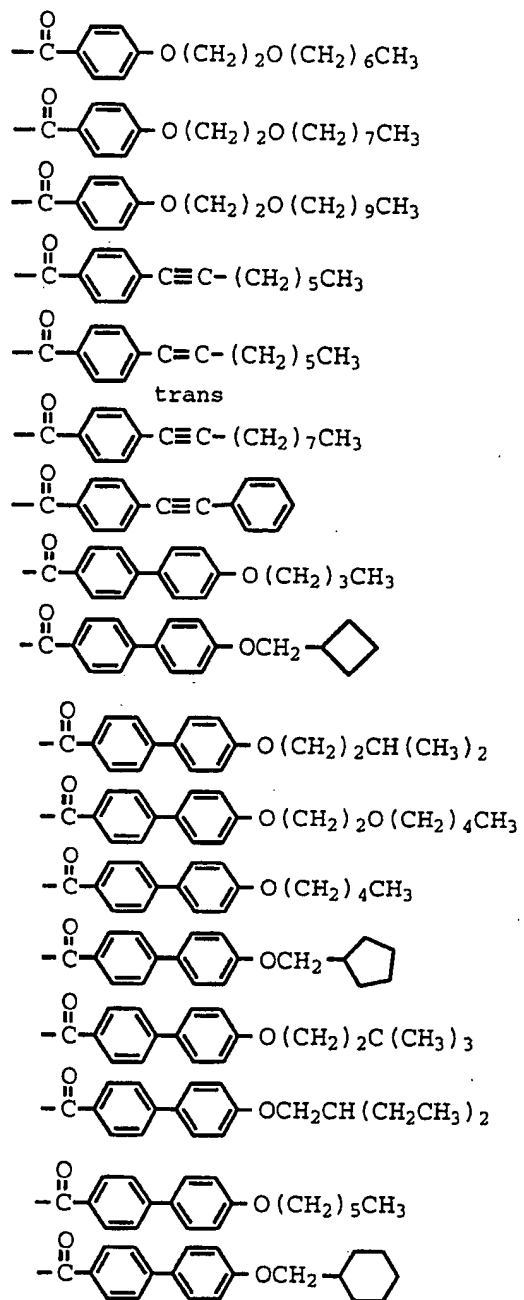
Examples of acyl groups, R₂

Table 1 (continued)
Examples of acyl groups, R₂

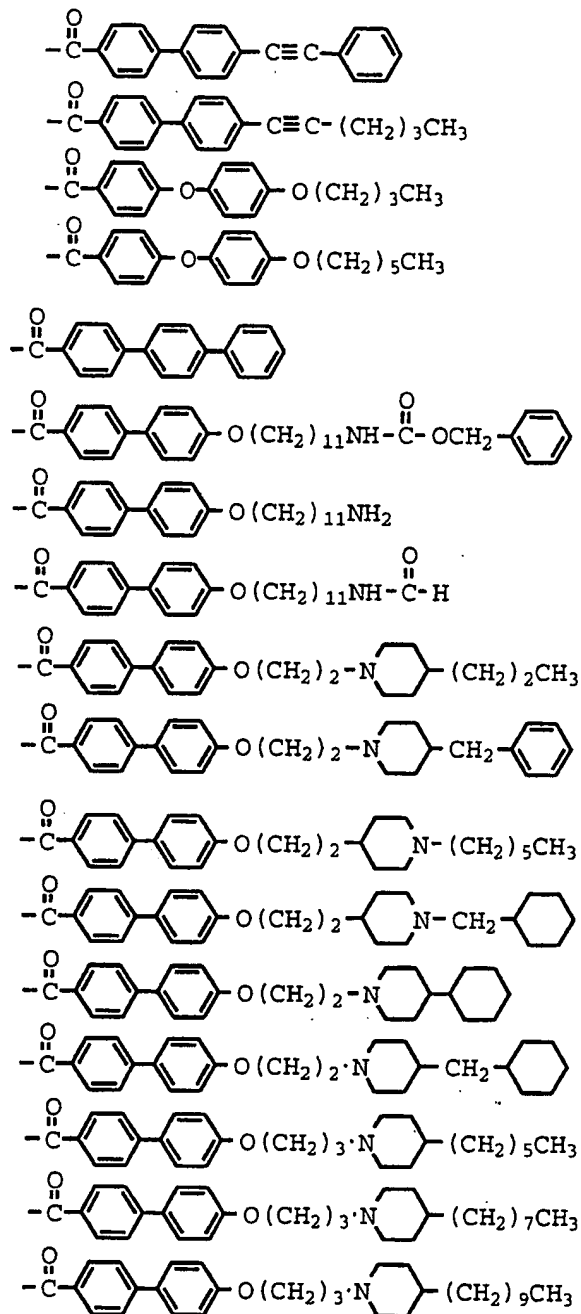


Table 1 (continued)

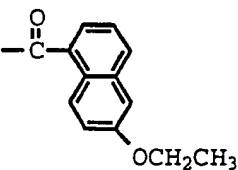
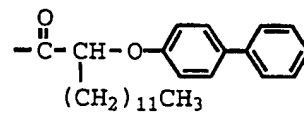
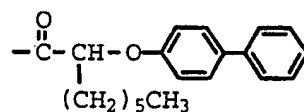
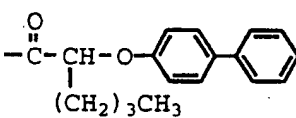
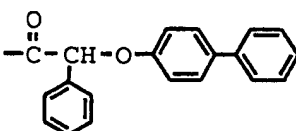
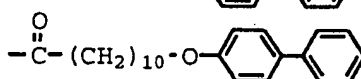
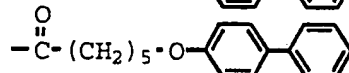
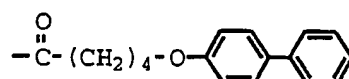
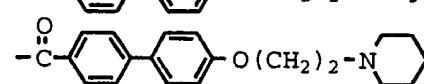
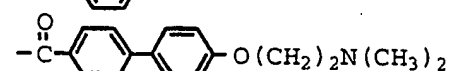
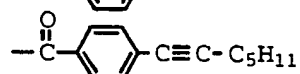
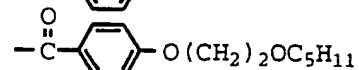
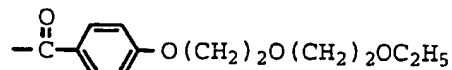
Examples of acyl groups, R₂

Table 1 (continued)
Examples of acyl groups, R₂

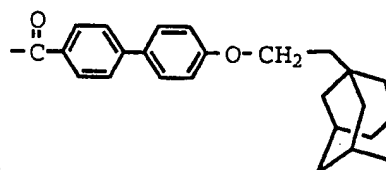
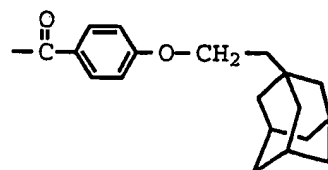
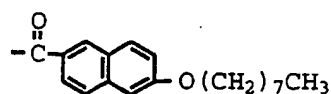
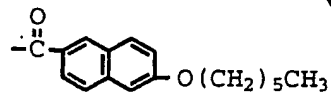
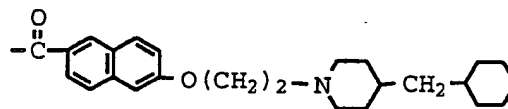
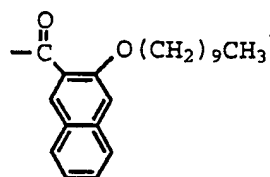
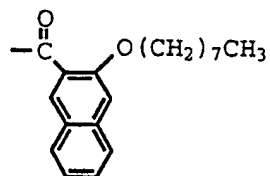
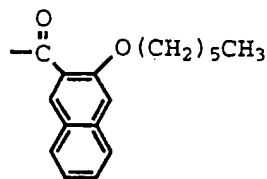
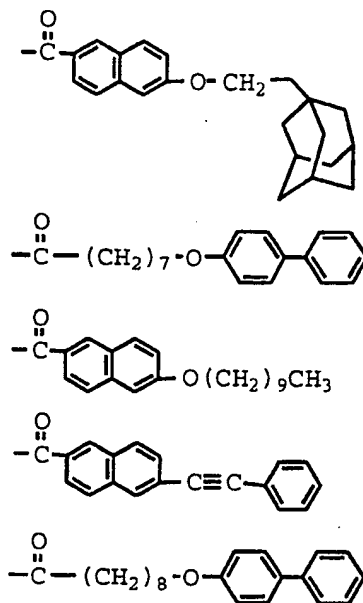
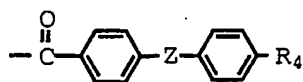


Table 1 (continued)
 Examples of acyl groups, R₂



5

Preferred acyl groups include those groups where R₂ is a group of the formula:



10

where Z is -C≡C- or a bond;

A) R₄ is hydrogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ alkynyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy, C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₃-C₁₂ cycloalkoxy, naphthyl, pyridyl, thienyl, benzothienyl, quinolyl or phenyl; or

15

B) R₄ is phenyl substituted by amino, C₁-C₁₂ alkylthio, halo, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ substituted alkyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, phenyl, substituted phenyl, or a group of

20

the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m, n and p are as defined above; or

5 C) R_4 is C_1-C_{12} alkoxy substituted with halo, C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, C_1-C_6 alkoxy, C_2-C_{12} alkynyl, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, formamido, C_2-C_{12} alkanoylamino, or phenyl substituted with a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m, n
10 and p are as defined above; or

D) R_4 is $-O-(CH_2)_r-W-R_5$;
r is 2, 3 or 4;
W is pyrrolidino, piperidino or piperazino;
15 R_5 is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl; or

E) R_4 is $-Y^1-R_6$;
 Y^1 is $-C\equiv C-$ or $-CH=CH-$;
20 R_6 is C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, C_3-C_{12} cycloalkenyl, naphthyl, benzothiazolyl, thienyl, indanyl, fluorenyl, or phenyl substituted with C_1-C_{12} alkylthio, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, halo(C_1-C_6 alkoxy) or a group of the formula
25 $-O-(CH_2)_r-W-R_5$ where r, W and R_5 are as defined above; or
 R_6 is phenyl substituted with a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m, n and p are as defined above; or

30 F) R_4 is C_1-C_{12} alkoxy substituted with a group of the formula $-NHC(O)R_7$;
 R_7 is C_1-C_6 alkoxy, or phenyl(C_1-C_6 alkoxy);
or a pharmaceutically acceptable salt thereof.

35 Of these preferred acyl groups, more preferred are those groups where:

A) R_4 is C_2 - C_{12} alkynyl, C_2 - C_{12} substituted alkynyl, C_1 - C_{12} alkoxy, C_3 - C_{12} cycloalkoxy, or phenyl; or

5 B) R_4 is phenyl substituted by C_1 - C_{12} alkoxy, or a group of the formula $-O-(CH_2)_2-O-(C_1-C_6 \text{ alkyl})$; or

C) R_4 is C_1 - C_{12} alkoxy substituted with C_3 - C_{12} cycloalkyl; or

10 D) R_4 is $-O-(CH_2)_r-W-R_5$;
 r is 2 or 3;
 W is piperidino;
 R_5 is hydrogen, C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, benzyl or C_3 - C_{12} cycloalkylmethyl; or

15 E) R_4 is $-Y^1-R_6$;
 Y^1 is $-C\equiv C-$;
 R_6 is phenyl substituted with C_1 - C_{12} alkylthio, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, halo(C_1 - C_6 alkoxy);
20 or R_6 is phenyl substituted with a group of the formula $-O-(CH_2)_r-W-R_5$ where r , W and R_5 are as defined above;

or R_6 is phenyl substituted with a group of the formula $-O-(CH_2)_2-O-(C_1-C_6 \text{ alkyl})$;
25 or a pharmaceutically acceptable salt thereof.

Of these acyl groups, especially preferred are those groups where:

30 R_4 is C_2 - C_{12} alkynyl, C_2 - C_{12} substituted alkynyl, C_1 - C_{12} alkoxy, or phenyl; or

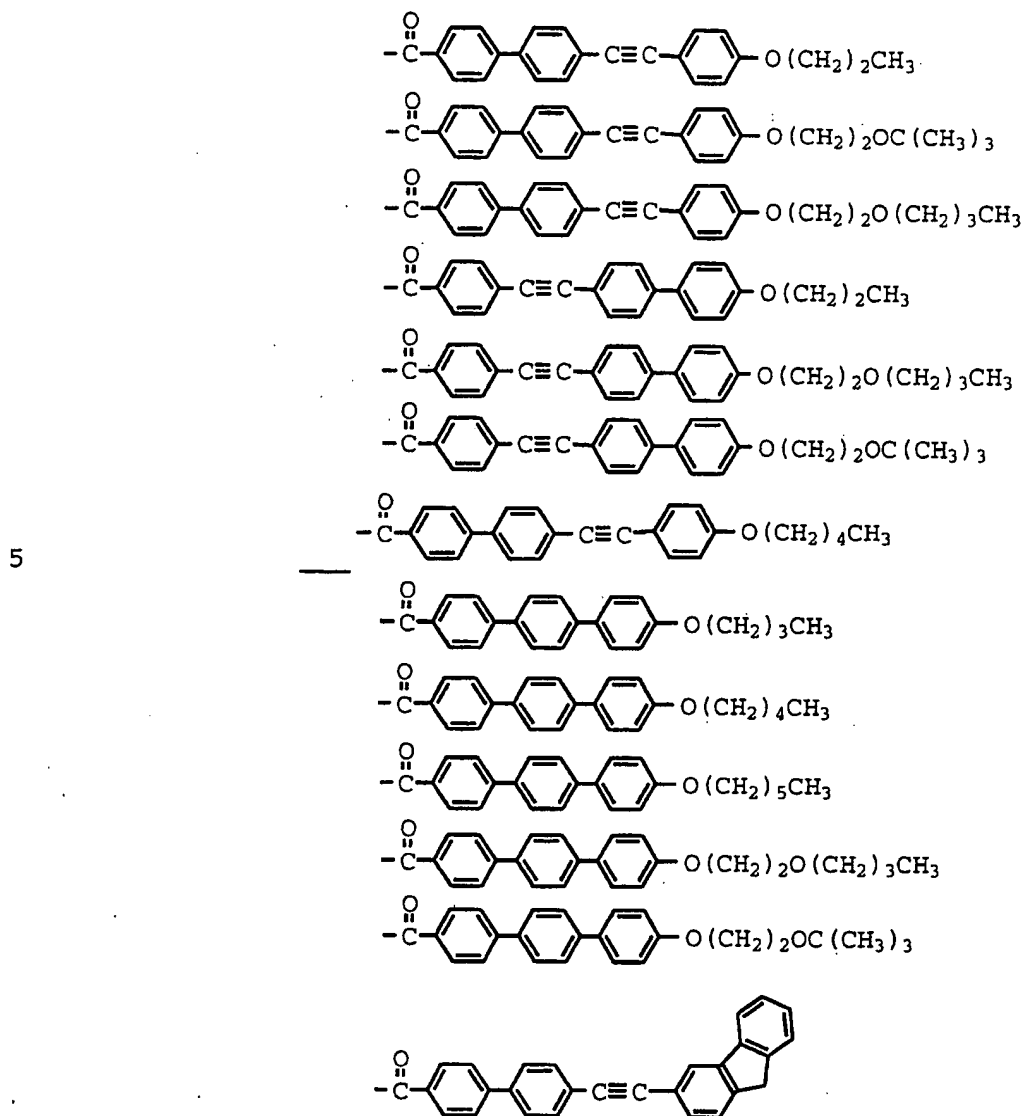
R_4 is phenyl substituted by C_1 - C_{12} alkoxy, or a group of the formula $-O-(CH_2)_2-O-(C_1-C_6 \text{ alkyl})$; or

R_4 is $-Y^1-R_6$;

Y^1 is $-C\equiv C-$;

35 R_6 is phenyl substituted with a group of the formula $-O-(CH_2)_2-O-(C_1-C_6 \text{ alkyl})$;
or a pharmaceutically acceptable salt thereof.

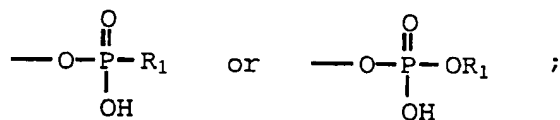
Of these acyl groups, the most preferred are where R_2 is one of the following groups:



10 Preferred compounds of this invention are those compounds of formula I where:

R' , R'' , and R''' are each methyl;
 R^{Y1} , R^{Y2} , R^{Y3} , R^{Y4} are each hydroxy;
 R^{X2} is hydroxy;

R₀ is hydroxy or a group of the formulae:



R₁ is methyl;

5 or a pharmaceutically acceptable salt thereof.

Of these compounds, more preferred are those compounds of formula I where:

R^{x1} is C₁-C₄ alkyl, benzyl, -CH₂CHOHCH₂OH,
 10 -CH₂COOH, -(CH₂)_bNR^{z1}R^{z2} or -(CH₂)₂POR^{z3}R^{z4};
 b is 2, 3, 4, 5 or 6;
 R^{z1} and R^{z2} are independently hydrogen or C₁-C₄
 alkyl; and
 R^{z3} and R^{z4} are independently hydrogen or
 15 methoxy;
 or a pharmaceutically acceptable salt thereof.

Of these compounds, further preferred are those compounds of formula I where:

R^{x1} is methyl, benzyl, -CH₂CHOHCH₂OH, -CH₂COOH,
 20 -(CH₂)₂NR^{z1}R^{z2} or -(CH₂)₂POR^{z3}R^{z4};
 R^{z1} and R^{z2} are independently hydrogen or
 methyl; and
 R^{z3} and R^{z4} are independently hydrogen or
 25 methoxy;
 or a pharmaceutically acceptable salt thereof.

Of these compounds, especially preferred are those compounds of formula I where:

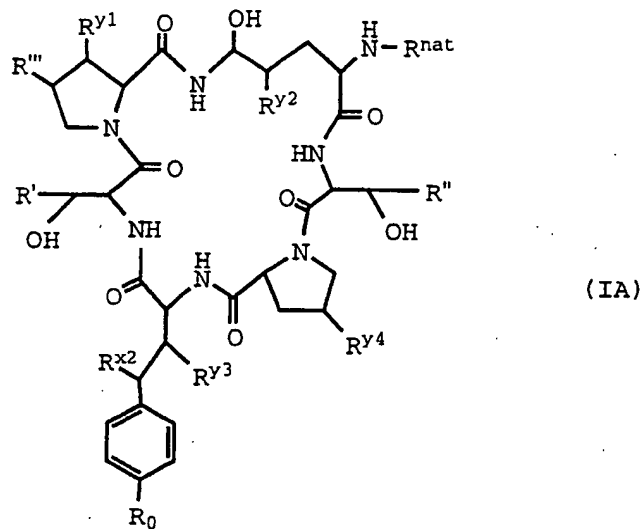
R^{x1} is -CH₂CHOHCH₂OH, -CH₂COOH or -(CH₂)₂POR^{z3}R^{z4};
 30 and
 R^{z3} and R^{z4} are independently hydrogen or
 methoxy;
 or a pharmaceutically acceptable salt thereof.

35

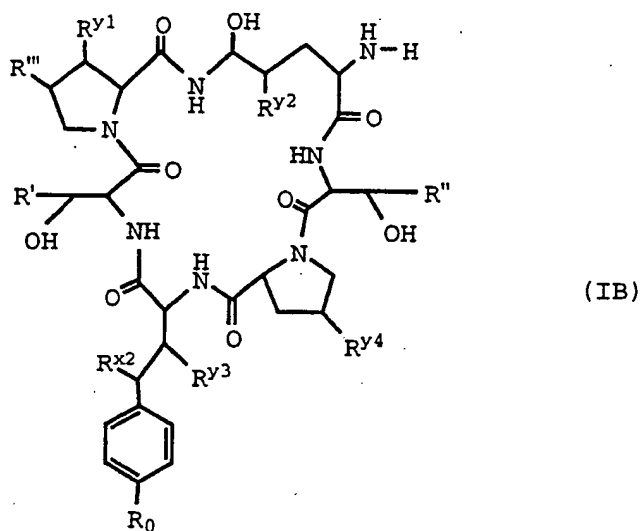
The compounds of formula I may be prepared according to Reaction Scheme I, as follows.

Reaction Scheme I

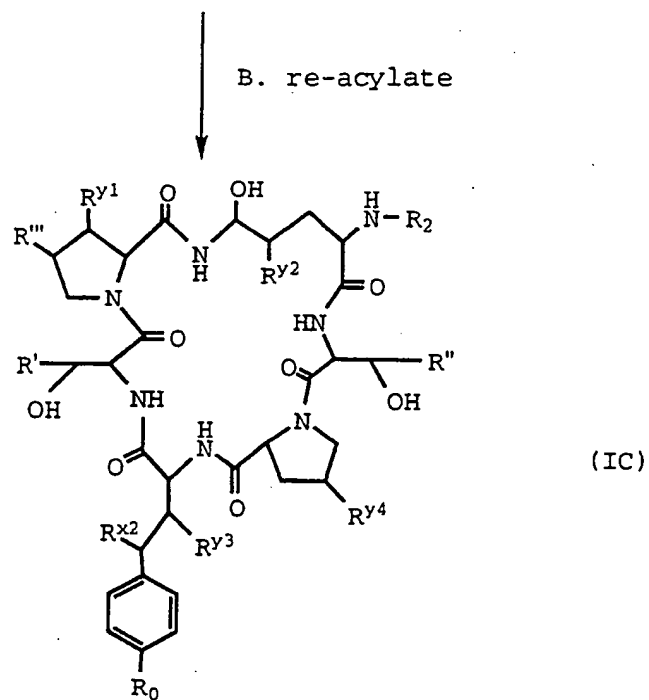
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A. deacylate

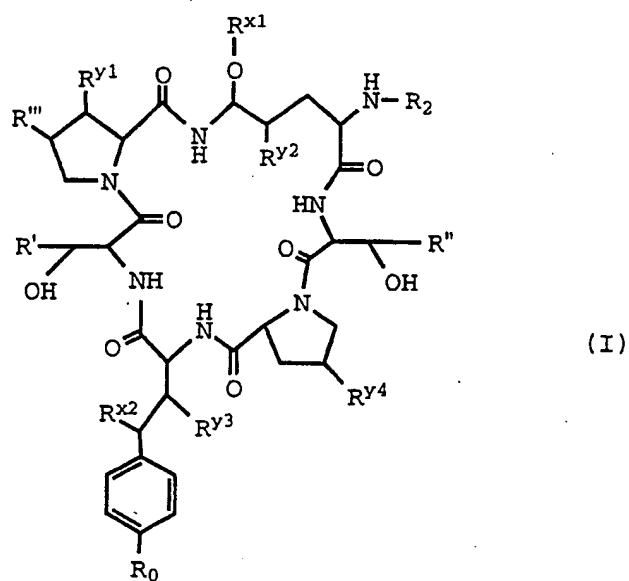


B. re-acylate



(IC)

C. Etherification



(I)

wherein:

R^{nat} is a naturally occurring cyclic peptide sidechain; and

5 R' , R'' , R''' , R^{x1} , R^{x2} , R^{y1} , R^{y2} , R^{y3} , R^{y4} , R_0 and R_2 are as defined above.

Reaction scheme I, above, is accomplished by carrying out reactions A-C, in order. Once a reaction is complete, the intermediate compound may be isolated by procedures well-known in the art, for example, the compound
10 may be crystallized or precipitated and then collected by filtration, or the reaction solvent may be removed by extraction, evaporation or decantation. The intermediate compound may be further purified, if desired, by common techniques such as crystallization or precipitation or
15 chromatography over solid supports such as silica gel, alumina and the like, before carrying out the next step of the reaction scheme.

In reaction IA, a naturally occurring cyclic peptide of the formula IA is deacylated using procedures
20 known in the art to provide an amino nucleus of formula IB. This reaction is typically carried out using enzymatic acylation by exposing the naturally occurring cyclic peptide to a deacylase enzyme. The deacylase enzyme may be obtained from the microorganism *Actinoplanes utahensis* and
25 used substantially as described in U.S. Patent Nos. 4,293,482 and 4,304,716, herein incorporated by reference. The deacylase enzyme may also be obtained from the *Pseudomonas* species. Deacylation may be accomplished using whole cells of *Actinoplanes utahensis* or *Pseudomonas* or the
30 crude or purified enzyme thereof or using an immobilized form of the enzyme. See European Patent Application No. 0 460 882 (December 11, 1991). Examples of naturally occurring cyclic peptides which may be used as starting materials include aculeacin (palmitoyl side chain),
35 tetrahydroechinocandin B (stearoyl side chain), mulundocandin (branched C_{15} side chain), S 31794/F1 (tetradecanoyl side chain), sporiofungin (C_{15} branched side

chain), FR901379 (palmitoyl side chain) and the like. A preferred naturally occurring cyclic peptide is echinocandin B (a compound of formula IA where R', R'', and R''' are each methyl, R^{x2}, RY¹, RY², RY³, RY⁴ and R₀ are each hydroxy and R₂ is linoleoyl).

In Reaction IB, the resulting amino nucleus is then re-acylated using procedures known in the art to provide a compound of formula I where R₂ is an acyl group as defined hereinabove.

For example, the amino nucleus may be acylated by reaction with an appropriately substituted acyl halide, preferably in the presence of an acid scavenger such as a tertiary amine, such as triethylamine. The reaction is typically carried out at a temperature of from about -20°C to about 25°C. Typical solvents for this reaction include polar aprotic solvents such as dioxane or dimethylformamide. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently solubilized to effect the desired reaction.

The amino nucleus may also be acylated by reaction with an appropriately substituted carboxylic acid, in the presence of a coupling agent. Typical coupling agents include dicyclohexylcarbodiimide (DCC), N,N'-carbonyldi-imidazole, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) and the like.

In addition, the amino nucleus may be acylated with an activated ester of a carboxylic acid such as an ester of a carboxylic acid of the formula R₂-COOH and p-nitrophenyl, 2,4,5-trichlorophenyl, hydroxybenzotriazole hydrate (HOBT·H₂O), pentafluorophenol, N-hydroxysuccinimide and the like. Preferred acylating moieties are the active esters of the carboxylic acid R₂-COOH such as 2,4,5-trichlorophenyl ester and benzotriazole ester. The

reaction is typically carried out for one to sixty five hours at a temperature from about 0°C to about 30°C in an aprotic solvent. The reaction is generally complete after about twenty four to forty eight hours when carried out at a temperature of from about 15°C to about 30°C. Typical solvents for this reaction are tetrahydrofuran and dimethylformamide or a mixture of such solvents. The amino nucleus is generally employed in equimolar proportions relative to the activated ester or with a slight excess of the amino nucleus.

In Reaction IC, a compound of formula IC is reacted with an appropriately substituted alcohol in the presence of an acid to provide a compound of formula I where R^{x1} is C_1-C_6 alkyl, benzyl, $-(CH_2)_2Si(CH_3)_3$, $-CH_2CH=CH_2$, $-(CH_2)_aCOOH$, $-(CH_2)_bNR^{z1}R^{z2}$, $-(CH_2)_cPOR^{z3}R^{z4}$ or $-[(CH_2)_2O]_d-(C_1-C_6)alkyl$. The reaction is typically carried out in a polar aprotic solvent such as dioxane, or dimethylsulfoxide at a temperature of from about 0°C to about 35°C, preferably at about room temperature. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently solubilized to effect the desired reaction. Preferred acids include p-toluenesulfonic acid, hydrochloric acid and camphorsulfonic acid.

The compounds of formula I where R^{x1} is $-(CH_2)_bNR^{z1}R^{z2}$ where R^{z1} and R^{z2} are hydrogen may be prepared via a protected compound wherein R^{x1} is $-(CH_2)_bNHR^a$ where R^a is an amino protecting group. The resultant protected compound may be deprotected according to procedures known in the art.

The compounds of formula I where R^{x1} is $-CH_2CHOHCH_2OH$ may be prepared by hydroxylating a compound of formula I where R^{x1} is $-CH_2CH=CH_2$ with osmium tetroxide in the presence of a catalyst at a temperature in the range of from about 0°C to about 40°C for about one to twenty four hours in a organic/aqueous solvent mixture, for example dioxane/water. Suitable catalysts include N-

methyilmorpholine N-oxide (NMO) and the like. Typical solvents suitable for use in this reaction include dimethylformamide, tetrahydrofuran, acetone and dioxane. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently solubilized to effect the desired reaction. The reaction is preferably conducted at a temperature in the range of from about 20°C to about 30°C for about eighteen to twenty four hours.

The compounds of formula I wherein R_0 is hydroxy may be phosphorylated by reaction with an appropriately substituted alkyl or phenyl phosphate to provide a compound of formula I where R_0 is $-OP(O)OH-R_1$ where R_1 is C_1-C_6 alkoxy or phenoxy, or by reaction with an appropriately substituted alkyl or phenyl phosphonic acid to provide a compound of formula I where R_0 is $-OP(O)OH-R_1$ where R_1 is C_1-C_6 alkyl, or an appropriately substituted phenyl or benzyl moiety. The phosphonic acid is typically used in an activated form, for example as a phosphonic halide, preferably a phosphonic chloride. The reaction is carried out in the presence of a base such as lithium trimethylsilanolate (LiOTMS), lithium bis(trimethylsilyl)amide (LHMDS), pyridine and the like. The reaction is typically carried out for up to one hour at a temperature from about -30°C to about 40°C in an aprotic solvent such as tetrahydrofuran and dimethylformamide. The reaction is generally complete in about fifteen minutes when carried out under these conditions. The phosphate or phosphonate reactant is generally employed in equimolar proportions to about a one mole excess relative to the amino nucleus in the presence of an equimolar or slight excess of the base.

The cyclic peptides used to make the compounds of the present invention may be prepared by fermentation of known microorganisms. For example, the cyclic peptide of formula IB where R' , R'' and R''' are methyl, R^{x2} is hydroxy and RY^1 , RY^2 , RY^3 , RY^4 and R_0 are each hydroxy (cyclic

nucleus corresponding to A-30912A) may be prepared using the procedure detailed in Abbott et al., U.S. Pat. Ser. No. 4,293,482, which is herein incorporated by reference. The cyclic peptide of formula IB where R', R" and R''' are methyl, R^{x2} is hydrogen and RY¹, RY², RY³ RY⁴ and R₀ are each hydroxy (cyclic nucleus corresponding to A-30912B) may be prepared using the procedure detailed in Abbott et al., U.S. Pat. Ser. No. 4,299,763, which is herein incorporated by reference. Aculeacin may be prepared using the procedure detailed in Mizuno et al., U.S. Pat. Ser. No. 3,978,210 which is herein incorporated by reference. The cyclic peptide of formula IB where R' is -CH₂C(O)NH₂, R" is methyl, R''' is hydrogen and R^{x1}, R^{x2}, RY¹, RY², RY³, RY⁴ and R₀ is hydroxy may be prepared by deacylating the cyclic peptide prepared using the procedure detailed in Shieh-Shung et al., U.S. Pat. Ser. No. 5,198,421, which is herein incorporated by reference.

The R₂-COOH precursor acids are prepared by hydrolyzing a nitrile of the formula R₂-CN or an ester of the formula R₂-COO(C₁-C₄ alkyl). The nitrile and ester intermediates may be prepared using procedures known in the art.

For example, the nitrile and ester intermediates where R₂ is an alkoxy aryl moiety may be prepared using Procedure A or Procedure B, described below.

Procedure A

One equivalent of an alkyl bromide, iodide, or p-toluenesulfonate is added to a mixture containing one equivalent of a base, such as potassium t-butoxide or potassium carbonate, and one equivalent of an hydroxy aryl compound in 200-300 ml of acetonitrile. The resulting reaction mixture is refluxed for approximately six hours and then concentrated in vacuo to provide a residue. This residue is dissolved in a mixture of diethyl ether and a 2N sodium hydroxide solution. The resulting layers are separated and the organic layer is dried over magnesium

sulfate, filtered and dried to provide the desired alkoxy aryl product.

Procedure B

One equivalent of diethylazodicarboxylate is added dropwise over ten minutes, at room temperature, to a mixture containing one equivalent of an hydroxy aryl compound, one equivalent of an alkyl alcohol and one equivalent of triphenylphosphine in 200-300 ml of tetrahydrofuran. After approximately seventeen hours, the solvent is removed in vacuo to provide a residue. This residue is dissolved in diethyl ether and the resulting mixture is washed with a 2N sodium hydroxide solution, dried over magnesium sulfate, filtered and concentrated to provide a product which is then crystallized from a diethyl ether/pentane mixture or, if the product contains a tertiary amine, the hydrochloride salt is formed and crystallized from a methanol/ethyl acetate mixture.

The nitrile and ester intermediates where R₂ is an alkynyl or alkenyl aryl moiety may be prepared using Procedure C, below.

Procedure C

A mixture containing two equivalents of triethylamine, 0.05 equivalent of palladium dichloride, 0.1 equivalent of triphenylphosphine, 0.025 equivalent of cuprous iodide and one equivalent of an alkyne or two equivalents of an alkene, is added to one equivalent of an aryl bromide, iodide, or trifluoromethanesulfonate in acetonitrile (600 ml/0.1 mol of aryl reactant), under nitrogen. The resulting mixture is refluxed for approximately seventeen hours and then the solvent is removed in vacuo to provide a residue. This residue is slurried in 300 ml of diethyl ether and then filtered to remove the resultant solids. The filtrate is washed with a 1N hydrochloric acid solution, dried over magnesium sulfate, filtered and then dried to provide the desired product.

The ester intermediates where R₂ is a terphenyl moiety may be prepared using Procedure D, below.

Procedure D

5 1. Formation of boronic acid reactant

Butyl lithium (1.2 equivalents) is added to one equivalent of a cold (-78°C) aryl halide in tetrahydrofuran. After approximately fifteen minutes, two equivalents of triisopropyl borate are added. After
10 approximately ten minutes, the reaction mixture is warmed to room temperature, and then quenched by the addition of water, followed by the addition of a 1N hydrochloric acid solution. The resulting layers are separated and the organic layer is concentrated in vacuo to provide a solid.
15 This solid is collected by filtration and then washed with hexane to provide a pure boronic acid product.

2. Formation of terphenyl ester

Tetrakis(triphenylphosphine)palladium (0.03 equivalent) is added to a mixture containing one
20 equivalent of an aryl boronic acid, 1.5 equivalents of potassium carbonate and one equivalent of methyl 4-iodobenzoate (or trichlorophenyl ester of iodobenzoate) in nitrogen-purged toluene. The resulting reaction mixture is refluxed for approximately seven hours and then decanted to
25 remove the potassium carbonate and dried in vacuo to provide a residue. This residue is triturated in acetonitrile and then filtered to provide the desired solid product.

30 The aryl nitriles and esters described above may be converted to the corresponding carboxylic acids by hydrolysis using Procedure E or Procedure F, below.

Procedure E

35 An aryl nitrile is dissolved in ethanol and an excess of 50% sodium hydroxide solution and refluxed for approximately two hours. Water is added to the resulting reaction mixture until a solid precipitates. This solid is

collected by filtration, added to a dioxane/6N hydrochloric acid mixture and the resulting mixture is refluxed for approximately seventeen hours. When the reaction is substantially complete, the carboxylic acid product is crystallized by the addition of water and then collected by filtration and dried *in vacuo*.

Procedure F

An excess of a 2N sodium hydroxide solution is added to an aryl ester in methanol, and the resulting solution is refluxed for approximately five hours and then acidified by the addition of excess hydrochloric acid. Water is added to the resulting reaction mixture until a solid (carboxylic acid) precipitates. The carboxylic acid is collected by filtration and dried *in vacuo*.

The carboxylic acids may be converted to the corresponding 2,4,5-trichlorophenyl esters using Procedure G, below. These activated esters are then used to acylate the amino nucleus, as described above in Reaction Scheme IC.

Procedure G

A mixture containing one equivalent of an aryl carboxylic acid, one equivalent of 2,4,5-trichlorophenol, and one equivalent of N,N'-dicyclohexylcarbodiimide (DCC) in methylene chloride is stirred for approximately seventeen hours and then filtered. The filtrate is concentrated to provide a residue. This residue is dissolved in diethyl ether, filtered, and pentane is added until crystallization begins. The crystalline product is collected by filtration and dried *in vacuo*.

The following Preparations and Examples further describe how to synthesize the compounds of the present invention. The terms melting point, proton nuclear magnetic resonance spectra, mass spectra, infrared spectra, ultraviolet spectra, elemental analysis, high performance liquid chromatography, and thin layer chromatography are

abbreviated "m.p.", "NMR", "MS", "IR", "UV", "Analysis",
"HPLC", and "TLC", respectively. In addition, the
absorption maxima listed for the IR spectra are only those
of interest and not all of the maxima observed.

5

Preparation 1

The following nitrile and ester intermediates
where R₂ is an alkoxy aryl moiety were prepared
substantially in accordance with Procedure A, detailed
above.

10

Table A








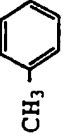
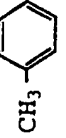
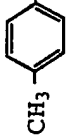
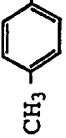

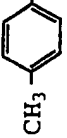
Alkyl halide or tosylate	mass (g)	Alkoxy aryl product	mass (g)
I-(CH ₂) ₃ CH ₃	9.4	CH ₃ (CH ₂) ₃ O-C ₆ H ₄ -C ₆ H ₄ -CN	3.2
CH ₃ -C ₆ H ₄ -SO ₃ -CH ₂ - 	12.3	 -CH ₂ O-C ₆ H ₄ -C ₆ H ₄ -CN	5.3
Br-(CH ₂) ₂ CH(CH ₃) ₂	7.7	(CH ₃) ₂ CH(CH ₂) ₂ O-C ₆ H ₄ -C ₆ H ₄ -CN	9.2
CH ₃ -C ₆ H ₄ -SO ₃ -(CH ₂) ₂ O(CH ₂) ₄ CH ₃	7.6	CH ₃ (CH ₂) ₄ O-(CH ₂) ₂ O-C ₆ H ₄ -C ₆ H ₄ -CN	4.8
Br-(CH ₂) ₄ CH ₃	15.3	CH ₃ (CH ₂) ₄ O-C ₆ H ₄ -C ₆ H ₄ -CN	20.3
CH ₃ -C ₆ H ₄ -SO ₃ -CH ₂ - 	13.0	 -CH ₂ O-C ₆ H ₄ -C ₆ H ₄ -CN	12.2
CH ₃ -C ₆ H ₄ -SO ₃ -(CH ₂) ₂ C(CH ₃) ₃	13.1	(CH ₃) ₃ C(CH ₂) ₂ O-C ₆ H ₄ -C ₆ H ₄ -CN	11.8
Br-CH ₂ CH(CH ₂ CH ₃) ₂	8.5	(CH ₂ CH ₃) ₂ CHCH ₂ O-C ₆ H ₄ -C ₆ H ₄ -CN	3.0
I-(CH ₂) ₅ CH ₃	10.8	CH ₃ (CH ₂) ₅ O-C ₆ H ₄ -C ₆ H ₄ -CN	11.4
Br-(CH ₂) ₂ - 	4.2	 -(CH ₂) ₂ O-C ₆ H ₄ -C ₆ H ₄ -CO ₂ CH ₃	4.5

Table A (continued)

Alkyl halide or tosylate	mass (g)	Alkoxy aryl product	mass (g)
 $\text{SO}_3 \cdot (\text{CH}_2)_2 \text{O} (\text{CH}_2)_6 \text{CH}_3$	23.4	$\text{CH}_3 (\text{CH}_2)_6 \text{O} \cdot (\text{CH}_2)_2 \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2 \text{CH}_2 \text{CH}_3$	20.9
 $\text{SO}_3 \cdot (\text{CH}_2)_2 \text{O} (\text{CH}_2)_7 \text{CH}_3$	25.8	$\text{CH}_3 (\text{CH}_2)_7 \text{O} \cdot (\text{CH}_2)_2 \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2 \text{CH}_2 \text{CH}_3$	7.9
 $\text{SO}_3 \cdot (\text{CH}_2)_2 \text{O} (\text{CH}_2)_9 \text{CH}_3$	27.1	$\text{CH}_3 (\text{CH}_2)_9 \text{O} \cdot (\text{CH}_2)_2 \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2 \text{CH}_2 \text{CH}_3$	21.0
$\text{I} \cdot (\text{CH}_2)_3 \text{CH}_3$	6.1	$\text{CH}_3 (\text{CH}_2)_3 \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2 \text{CH}_3$	12.3
$\text{I} \cdot (\text{CH}_2)_5 \text{CH}_3$	4.3	$\text{CH}_3 (\text{CH}_2)_5 \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2 \text{CH}_3$	4.7
$\text{I} \cdot (\text{CH}_2)_2 \text{CH}_3$	2.6	$\text{CH}_3 (\text{CH}_2)_2 \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{C} \equiv \text{C} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2 \text{CH}_3$	4.4
 $\text{SO}_3 \cdot (\text{CH}_2)_2 \text{O} (\text{CH}_2)_3 \text{CH}_3$	2.7	$\text{CH}_3 (\text{CH}_2)_3 \text{O} \cdot (\text{CH}_2)_2 \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{C} \equiv \text{C} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2 \text{CH}_3$	2.6
 $\text{SO}_3 \cdot (\text{CH}_2)_2 \text{OC} (\text{CH}_3)_3$	2.7	$(\text{CH}_3)_3 \text{CO} \cdot (\text{CH}_2)_2 \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{C} \equiv \text{C} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2 \text{CH}_3$	2.6
$\text{I} \cdot (\text{CH}_2)_2 \text{CH}_3$	3.8	$\text{CH}_3 (\text{CH}_2)_2 \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{C} \equiv \text{C} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2 \text{CH}_3$	1.4
 $\text{SO}_3 \cdot (\text{CH}_2)_2 \text{O} (\text{CH}_2)_3 \text{CH}_3$	3.6	$\text{CH}_3 (\text{CH}_2)_3 \text{O} \cdot (\text{CH}_2)_2 \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{C} \equiv \text{C} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2 \text{CH}_3$	5.1
 $\text{SO}_3 \cdot (\text{CH}_2)_2 \text{OC} (\text{CH}_3)_3$	4.9	$(\text{CH}_3)_3 \text{CO} \cdot (\text{CH}_2)_2 \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{C} \equiv \text{C} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2 \text{CH}_3$	5.2

Preparation 2

The following nitrile and ester intermediates where R₂ is an alkoxy aryl moiety were prepared substantially in accordance with Procedure B, detailed above.

Table B

Alkyl alcohol	mass (g)	Alkoxy Aryl Product	mass (g)
$\text{HO}-(\text{CH}_2)_2-\text{N}(\text{CH}_2)_2\text{CH}_3$	3.6	$\text{CH}_3(\text{CH}_2)_2-\text{N}(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	6.2
$\text{HO}-(\text{CH}_2)_2-\text{N}(\text{CH}_2)_2\text{CH}_2-\text{C}_6\text{H}_5$	6.1	$\text{C}_6\text{H}_5-\text{CH}_2-\text{N}(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	4.3
$\text{HO}-(\text{CH}_2)_2-\text{N}-(\text{CH}_2)_5\text{CH}_3$	0.5	$\text{CH}_3(\text{CH}_2)_5-\text{N}(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	0.8
$\text{HO}-(\text{CH}_2)_2-\text{N}(\text{CH}_2)_2\text{CH}_2-\text{C}_6\text{H}_{10}$	0.5	$\text{C}_6\text{H}_{10}-\text{CH}_2-\text{N}(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	0.5
$\text{HO}-(\text{CH}_2)_2-\text{N}(\text{CH}_2)_2\text{C}_6\text{H}_{10}$	2.3	$\text{C}_6\text{H}_{10}-\text{N}(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	1.3
$\text{HO}-(\text{CH}_2)_2-\text{N}(\text{CH}_2)_2\text{CH}_2-\text{C}_6\text{H}_{10}$	9.3	$\text{C}_6\text{H}_{10}-\text{CH}_2-\text{N}(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	9.6
$\text{HO}-\text{CH}_2-\text{C}_6\text{H}_4-(\text{CH}_2)_3\text{CH}_3$	10.0	$\text{CH}_3(\text{CH}_2)_3-\text{CH}_2\text{O}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_2\text{CH}_3$	13.6

Preparation 3

The following ester intermediates where R_2 is an alkynyl or alkenyl aryl moiety were prepared substantially in accordance with Procedure C, detailed above.

Table C

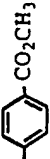
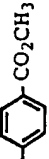

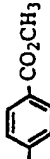
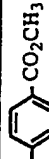
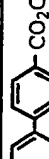
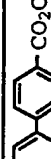
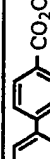


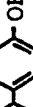
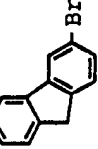
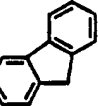
Alkene or alkyne	mass (g)	Aryl halide	mass (g)	Alkenyl or alkynyl aryl product	mass (g)
$\text{HC}\equiv\text{C}-(\text{CH}_2)_5\text{CH}_3$	12.1		28.8	$\text{CH}_3(\text{CH}_2)_5-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	26.2
$\text{HC}\equiv\text{C}-(\text{CF}_2)_5\text{CH}_3$	6.1		14.4	$\text{CH}_3(\text{CH}_2)_5-\text{CH}=\text{CH}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$ (trans)	0.6
$\text{HC}\equiv\text{C}-(\text{CH}_2)_7\text{CH}_3$	15.2		28.8	$\text{CH}_3(\text{CH}_2)_7-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	28.1
$\text{HC}\equiv\text{C}-\text{C}_6\text{H}_5$	1.9		5.1	$\text{C}_6\text{H}_5-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	1.9
$\text{HC}\equiv\text{C}-\text{Si}(\text{CH}_3)_3$	4.3		11.5	$(\text{CH}_3)_3\text{Si}-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	11.2
$\text{HC}\equiv\text{C}-\text{C}_6\text{H}_4$	1.8		6.0	$\text{C}_6\text{H}_4-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	2.6
$\text{HC}\equiv\text{C}-(\text{CH}_2)_3\text{CH}_3$	1.4		6.0	$\text{CH}_3(\text{CH}_2)_3-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	5.1
$\text{HC}\equiv\text{C}-\text{Si}(\text{CH}_3)_3$	10.9		40.0	$(\text{CH}_3)_3\text{Si}-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	23.3

Table C (continued)

Alkene or alkyne	mass (g)	Arvl halide	mass (g)	Alkenyl or alkynyl aryl product	mass (g)
$\text{HC}\equiv\text{C}-(\text{CH}_2)_7\text{CH}_3$	7.6		11.3	$\text{CH}_3(\text{CH}_2)_7-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{O}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	11.4
$\text{HC}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	10.5		9.7	$\text{HO}-\text{C}_6\text{H}_4-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	10.2
$\text{HC}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	22.2		34.4	$\text{HO}-\text{C}_6\text{H}_4-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	19.4
$\text{HC}\equiv\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_3$	1.2		1.2		1.5

Preparation 4

The following ester intermediates where R₂ is a terphenyl moiety were prepared substantially in accordance with Procedure D, detailed above.

5

Table D.1

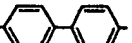
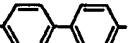
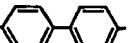
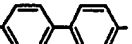
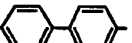

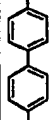

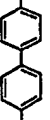
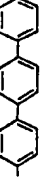
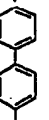
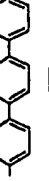
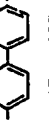
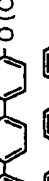


<u>Aryl halide</u> (R ^D is bromide)	<u>mass</u> (g)	<u>Boronic acid</u> <u>reactant</u> (R ^D is B(OH) ₂ mass (g))
R ^D -  O(CH ₂) ₃ CH ₃	10.6	6.1
R ^D -  O(CH ₂) ₄ CH ₃	31.0	12.0
R ^D -  O(CH ₂) ₅ CH ₃	10.9	4.1
R ^D -  O(CH ₂) ₂ -O(CH ₂) ₃ CH ₃	13.6	5.7
R ^D -  O(CH ₂) ₂ -OC(CH ₃) ₃	5.0	1.9

Table D.2

Boronic acid reactant	mass (g)	CH_3CO_2 - 	mass (g)	Product	mass (g)
$(\text{HO})_2\text{B}$ -  - $\text{O}(\text{CH}_2)_3\text{CH}_3$	5.0	3.2	CH_3CO_2 -  - $\text{O}(\text{CH}_2)_3\text{CH}_3$	4.2	
$(\text{HO})_2\text{B}$ -  - $\text{O}(\text{CH}_2)_4\text{CH}_3$	6.0	3.7	CH_3CO_2 -  - $\text{O}(\text{CH}_2)_4\text{CH}_3$	5.2	
$(\text{HO})_2\text{B}$ -  - $\text{O}(\text{CH}_2)_5\text{CH}_3$	3.4	2.8	CH_3CO_2 -  - $\text{O}(\text{CH}_2)_5\text{CH}_3$	3.5	
$(\text{HO})_2\text{B}$ -  - $\text{O}(\text{CH}_2)_2-\text{O}(\text{CH}_2)_3\text{CH}_3$	3.7	3.6	CH_3CO_2 -  - $\text{O}(\text{CH}_2)_2-\text{O}(\text{CH}_2)_3\text{CH}_3$	3.7	
$(\text{HO})_2\text{B}$ -  - $\text{O}(\text{CH}_2)_2-\text{OC}(\text{CH}_3)_3$	1.8	1.5	CH_3CO_2 -  - $\text{O}(\text{CH}_2)_2-\text{OC}(\text{CH}_3)_3$	2.2	

Preparation 5

5 The following activated esters were prepared
substantially in accordance with Procedure G, detailed
above.

Table G

Carboxylic acid	mass (g)	
	mass (g)	activated ester (2,4,5-trichlorophenyl ester)
$\text{CH}_3(\text{CH}_2)_3\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	1.9	1.8
$\text{Cyclopentyl-CH}_2\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	4.2	4.4
$(\text{CH}_3)_2\text{CH}(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	3.0	1.7
$\text{CH}_3(\text{CH}_2)_4\text{O}-(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	2.2	1.3
$\text{CH}_3(\text{CH}_2)_4\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	5.7	5.1
$\text{Cyclopentyl-CH}_2\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	4.4	3.1
$(\text{CH}_3)_3\text{C}(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	2.3	2.6
$(\text{CH}_3\text{CH}_2)_2\text{CHCH}_2\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	1.5	0.8
$\text{CH}_3(\text{CH}_2)_5\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	5.3	4.8
$\text{Cyclohexyl}-(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	3.1	1.0
$\text{CH}_3(\text{CH}_2)_6\text{O}-(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	5.6	2.9
$\text{CH}_3(\text{CH}_2)_7\text{O}-(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	7.8	6.6

Table G (continued)

Carboxylic acid	mass (g)	mass (g) activated ester (2,4,5-trichlorophenyl ester)
$\text{CH}_3(\text{CH}_2)_9\text{O}-(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	6.4	1.3
$\text{CH}_3(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{CH}_2\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	4.0	3.2
$\text{CH}_3(\text{CH}_2)_3\text{O}-\text{C}_6\text{H}_4-\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	5.8	1.4
$\text{CH}_3(\text{CH}_2)_5\text{O}-\text{C}_6\text{H}_4-\text{O}-\text{C}_6\text{H}_4-\text{COOH}$	3.8	2.4
$\text{CH}_3(\text{CH}_2)_3\text{O}-\text{C}_6\text{H}_4-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{COOH}$	2.9	2.5
$\text{CH}_3(\text{CH}_2)_3\text{O}-(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{COOH}$	2.0	1.5
$(\text{CH}_3)_3\text{CO}-(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{COOH}$	2.0	1.3
$\text{CH}_3(\text{CH}_2)_3\text{O}-\text{C}_6\text{H}_4-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{COOH}$	6.5	5.2
$\text{CH}_3(\text{CH}_2)_3\text{O}-(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{COOH}$	4.9	5.2
$(\text{CH}_3)_3\text{CO}-(\text{CH}_2)_2\text{O}-\text{C}_6\text{H}_4-\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-\text{COOH}$	4.6	2.1

Table G (continued)



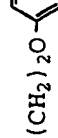
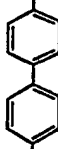

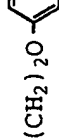

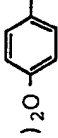

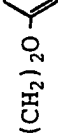

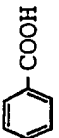
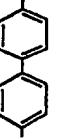
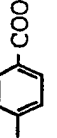
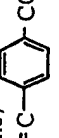
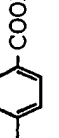


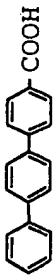
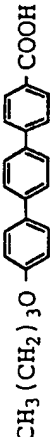
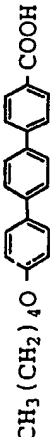
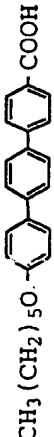
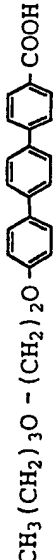

Carboxylic acid	mass (g)	mass (g) activated ester (2,4,5-trichlorophenyl ester)
$\text{CH}_3(\text{CH}_2)_2\text{-N}-(\text{CH}_2)_2\text{-O-}$  -COOH	3.3	1.5
 $\text{-CH}_2\text{-N}-(\text{CH}_2)_2\text{-O-}$  -COOH	3.0	2.3
$\text{CH}_3(\text{CH}_2)_5\text{-N}-(\text{CH}_2)_2\text{-O-}$  -COOH	1.0	1.0
 $\text{-CH}_2\text{-N}-(\text{CH}_2)_2\text{-O-}$  -COOH	2.0	0.8
 $\text{-N}-(\text{CH}_2)_2\text{-O-}$  -COOH	7.2	0.8
 $\text{-CH}_2\text{-N}-(\text{CH}_2)_2\text{-O-}$  -COOH	7.5	7.3
 $\text{-C}\equiv\text{C-}$  -COOH	2.0	0.6
$\text{CH}_3(\text{CH}_2)_3\text{-C}\equiv\text{C-}$  -COOH	1.1	0.6
$\text{CH}_3(\text{CH}_2)_5\text{-C}\equiv\text{C-}$  -COOH	4.6	3.5
$\text{CH}_3(\text{CH}_2)_5\text{-CH=CH-}$ ^(trans)  -COOH	1.2	0.5
$\text{CH}_3(\text{CH}_2)_7\text{-C}\equiv\text{C-}$  -COOH	11.1	13.2

Table G (continued)

Carboxylic acid	mass (g)	mass (g) activated ester (2,4,5-trichlorophenyl ester)
	1.5	1.5
	8.3	13.2
	0.8	1.2
	3.3	4.8
	3.0	2.5
	2.3	3.9
	3.3	4.4
	1.3	1.9

Example 1N-Acylation of Cyclic Peptide Nuclei

The N-acyl cyclic peptide derivatives listed in Table 2, below were prepared by dissolving Echinocandin B (A-30912A) nucleus (compound of formula IB where R', R" and R''' are each methyl, and R^{x2}, RY¹, RY², RY³, RY⁴ and R₀ are each hydroxy), and the activated ester (2,4,5-trichlorophenol ester) intermediates, described in Preparation 6, in 25-50 ml of dimethylformamide. The resultant reaction mixture was stirred for approximately 17-65 hours at room temperature and then the solvent was removed *in vacuo* to provide a residue. This residue was slurried in ether, collected by filtration, washed with methylene chloride and then dissolved in methanol or a 1:1 (v/v) acetonitrile/water mixture. The resultant solution is subjected to reverse phase HPLC (C18; eluent of 20-40% aqueous acetonitrile containing 0.5% monobasic ammonium phosphate (w/v); 20 ml/min.; 230 nm). After removing the unreacted A30912A nucleus, the desired product is eluted from the column using an eluent of aqueous acetonitrile. The fractions containing the desired product are combined and then concentrated *in vacuo* or lyophilized to provide the desired acylated nucleus. The purity (percentage) may be analyzed using reverse phase HPLC (C18; 40% aqueous acetonitrile containing 0.5% monobasic ammonium phosphate (w/v); 2 ml/min; 230 nm) and MS (FAB).

For example, the compound depicted in Table 2II, below, was prepared substantially according to this procedure, using 348.1 g (60.2 mmol) of the A30912A nucleus, 26.0 g (48.2 mmol) of the 2,4,5-trichlorophenol ester of [(4"-pentyloxy)-1,1':4',1"-terphenyl]-4-carboxylic acid in 8.5 liter of dimethylformamide. The resultant reaction mixture was allowed to react for approximately forty eight hours and then concentrated *in vacuo* and purified using HPLC to provide 18 g of compound 2II.

MS (FAB): 1140.5103 (M⁺¹).



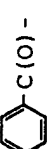
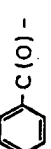

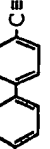
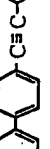

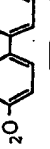
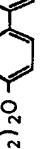
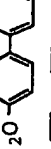





Compounds A-PP (listed in Table 2 below) were prepared substantially as described above.

Table 2

Ex. No.	R ₂	Ester (mg)	A30912A Nucleus (g)	Product (mg)	MS (FAB)	HPLC R _T (min)
2A		561	1.0	235	1072*	4.08
2B		576	1.0	294	1062*	4.46
2C		579	1.0	355	1086*	5.75
2D		634	1.0	359	1130*	5.79
2E		289	0.5	81	1083*	6.08
2F		594	1.0	295	1098*	6.44
2G		596	1.0	270	1100*	8.15
2H		596	1.0	359	1100*	9.13
2I		596	1.0	301	1100*	10.24
2J		629	1.0	180	1104**	--
2K		287	0.5	110	1082*	4.52
2L		593	1.0	307	1096*	7.28

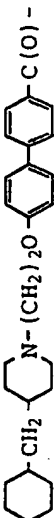
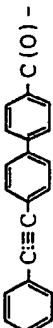


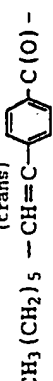




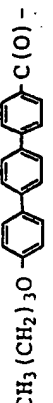
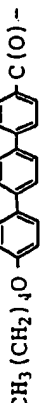
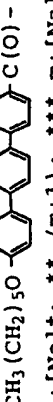
* (m-1)+[Na]⁺; ** (m+1); *** m+[Na]⁺; † m+1; †† m+[Li]⁺.

Table 2 (continued)

Ex. No.	R ₂	Ester (mg)	A30912A Nucleus (g)	Product (mg)	MS (FAB)	HPLC R _T (min)
2M	CH ₃ (CH ₂) ₉ O-(CH ₂) ₂ O-  -C(O)-	313	0.5	104	1124*	19.04
2N	CH ₃ (CH ₂) ₃ -  -CH ₂ O-  -C(O)-	579	1.0	293	1032*	6.14
2O	CH ₃ (CH ₂) ₃ O-  -O-  -C(O)-	291	0.5	98	1088*	3.96
2P	CH ₃ (CH ₂) ₅ O-  -O-  -C(O)-	616	1.0	341	1116*	11.56
2Q	CH ₃ (CH ₂) ₂ O-  -C≡C-  -C(O)-	2400	3.2	3000	1194.5213†	--
2R	CH ₃ (CH ₂) ₃ O-(CH ₂) ₂ O-  -C≡C-  -C(O)-	1300	1.5	2400	1194.5247†	--
2S	(CH ₃) ₃ CO-(CH ₂) ₂ O-  -C≡C-  -C(O)-	4600	7.4	1300	1126.5025†	--
2T	CH ₃ (CH ₂) ₂ -  -N-(CH ₂) ₂ O-  -C(O)-	683	1.0	384	1147**	1.92
2U	 -CH ₂ - -N-(CH ₂) ₂ O- -C(O)-	1490	2.0	116	1195**	2.06
2V	CH ₃ (CH ₂) ₅ -N-(CH ₂) ₂ O- -C(O)-	1000	1.2	194	1190***	2.41
2W	-CH ₂ -N-(CH ₂) ₂ O- -C(O)-	734	0.9	303	1202*	2.21
2X	-N-(CH ₂) ₂ O- -C(O)-	810	1.0	230	1187**	2.52


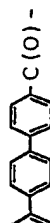
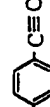
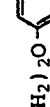
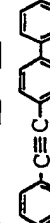
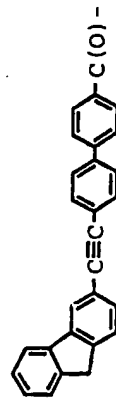
* (m-1)+[Na]⁺; ** (m+1); *** m+[Na]⁺; † m+1; ‡ m+[Li]⁺.

Table 2 (continued)

Ex. No.	R ₂	Ester (mg)	A30912A Nucleus (g)	Product (mg)	MS (FAB)	HPLC R _T (min)
2Y		750	1.0	126	1201**	3.50
2Z		596	1.0	190	1078**	6.30
2AA		571	1.0	295	1058**	7.91
2BB		511	1.0	322	1032*	5.10
2CC		514	1.0	287	1034*	6.14
2DD		546	1.0	285	1060*	12.48
2EE		501	1.0	218	1002**	2.53
2FF		534	1.0	215	1050***	7.59
2GG		566	1.0	81	1054**	3.89
2HH		4600	7.4	1300	1126.5025†	--
2II		2500	3.7	5100	1140.5103†	--
2JJ		3500	5.0	1400	1154.5343††	--

* (m-1)+[Na]⁺; ** (m+1); *** m+[Na]⁺; † m+1; †† m+[Li]⁺.

Table 2 (continued)

Ex. No.	R ₂	Ester (mg)	A30912A Nucleus (g)	Product (mg)	MS (FAB)	HPLC R _T (min)
2KK	CH ₃ (CH ₂) ₃ O-(CH ₂) ₂ O-  -C(O)-	4400	6.7	6500	1170.5234†	--
2LL	(CH ₃) ₃ CO-(CH ₂) ₂ O-  -C(O)-	1900	2.9	1400	1170.5261†	--
2MM	CH ₃ (CH ₂) ₂ O-  -C(O)-	5200	6.9	1400	1142.4951†	--
2NN	(CH ₃) ₃ CO-(CH ₂) ₂ O-  -C(O)-	2100	2.5	2000	1200.5336†	--
200	CH ₃ (CH ₂) ₃ O-(CH ₂) ₂ O-  -C(O)-	5200	6.4	1100	1194.5282†	--
2PP	 -C(O)-	1800	2.6	200	1166.4758†	--

* (m-1)+[Na]⁺; ** (m+1); *** m+[Na]⁺; † m+1; †† m+[Li]⁺.

Example 2

- 5 A. Preparation of the compound where R', R" and R''' are
 each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each
 hydroxy, R₂ is the acyl group depicted in Table 2Z and R^{x1}
 is prop-2-enyl

To an anhydrous solution containing 0.1 g
(0.09 mmol) of the compound depicted in Table 2Z and 631 µl
10 (9 mmol) of 3-hydroxypropene in 10 ml of anhydrous dioxane,
was added approximately 2 mg of p-toluenesulfonic acid.
When the reaction was substantially complete, as indicated
by thin layer chromatography (TLC), approximately 1 ml of a
saturated sodium bicarbonate solution was added to the
15 reaction mixture. The resultant mixture was concentrated
in vacuo to provide a solid. This solid was washed on a
fritted funnel with water and then removed using methanol
and the resulting mixture was purified using reverse phase
preparative HPLC (eluent of 60% aqueous acetonitrile, 75
20 ml/min.; 290 nm) to provide 88 mg of a white powder.

- B. Preparation of the compound where R', R" and R''' are
 each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each
 hydroxy, R₂ is the acyl group depicted in Table 2Z and
25 R^{x1} is 2,3-dihydroxypropyl

To a cold (0°C) solution of the compound of
Example 2A in a 1:1 mixture of dioxane and water, was added
4-methylmorpholine 4-oxide monohydrate (NMO) followed by
osmium tetroxide. An excess of sodium meta-bisulfite was
30 added and the resultant mixture was allowed to react for
approximately five hours. The reaction mixture was allowed
to warm to room temperature and then reacted for
approximately sixteen hours. The resultant mixture was
filtered and the filtrate was concentrated in vacuo to
35 provide a residue. This residue was redissolved in
methanol and then filtered through a fritted glass funnel.
The filtrate was concentrated in vacuo to provide a
residue. This residue was redissolved in a
methanol/acetonitrile/water mixture and the desired

compound was isolated using reverse phase preparative HPLC (eluent of 60% aqueous acetonitrile, 75 ml/min.; 290 nm).

Yield: 21 mg.

MS(FAB): Calcd: 1152.4777;

5 Found: 1152.4826

Example 3

10 A. Preparation of the compound where R', R" and R''' are each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R^{x1} is prop-2-enyl

The subtitled compound was prepared substantially in accordance with the procedure detailed in
15 Example 2A, using 1.0 g (0.88 mmol) of the compound depicted in Table 2II, 5.0 g (86.2 mmol) of 3-hydroxypropene and 8.3 mg (0.044 mmol) of p-toluenesulfonic acid (5 mol percent) in 100 ml of anhydrous dioxane.
MS(FAB): 1186.5 (M+Li).

20 B. Preparation of the compound where R', R" and R''' are each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R^{x1} is 2,3-dihydroxypropyl

25 The subtitled compound was prepared substantially in accordance with the procedure detailed in Example 2B, using the compound of Example 3A, a catalytic amount of osmium tetroxide and 4-methylmorpholine 4-oxide monohydrate in a 1:1 mixture of dioxane and water. The
30 desired compound was isolated using reverse phase preparative HPLC (eluent of 45% aqueous acetonitrile, 50 ml/min.; 290 nm).
Yield: 200 mg.
MS(FAB): 1235.5 (M+Na).

35

Example 4

- 5 A. Preparation of the compound where R', R" and R''' are each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R^{x1} is 4-(benzyloxycarbonylamino)butyl

10 To a solution containing 557.2 mg (0.501 mmol) of the compound depicted in Table 2II and 1.1188 g (5.02 mmol) of 4-(benzyloxycarbonylamino)butanol in 50 ml of dioxane, was added a catalytic amount (approximately 10 mol percent) of p-toluenesulfonic acid. When the reaction was substantially complete, as indicated by HPLC, the reaction was quenched with solid sodium bicarbonate. The resultant reaction mixture was concentrated in vacuo to provide a solid which was used without further purification.

15 MS(FAB): 1368.1 (M+Na).

- 20 B. Preparation of the compound where R', R" and R''' are each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R^{x1} is 4-aminobutyl

25 To a mixture of the compound from Example 4A in a 1:1 mixture of methanol and water, was added a catalytic amount (10 mol percent) of 10% palladium-on-carbon and two drops of glacial acetic acid. The resultant reaction was allowed to react under 1 atmosphere of hydrogen (gas). When the reaction was substantially complete, as indicated by HPLC, the reaction mixture was filtered. The filtrate was concentrated in vacuo to provide the desired subtitled compound.

30 Yield: 78 mg.
MS(FAB): 1211.5 (M⁺).

Example 5

5 A. Preparation of the compound where R', R" and R''' are each methyl, R_{x2}, R_{y1}, R_{y2}, R_{y3}, R_{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R_{x1} is 6-(benzyloxycarbonylamino)hexyl

10 The desired subtitled compound was prepared substantially in accordance with the procedure detailed in Example 4A, using 553.2 mg (0.497 mmol) of the compound depicted in Table 2II, 1.1190 g (4.458 mmol) of 6-(benzyloxycarbonylamino)hexanol and a catalytic amount (approximately 10 mol percent) of p-toluenesulfonic acid in 50 ml of dioxane to provide a solid which was used without further purification.

15 MS(FAB): 1395.7 (M+Na).

20 B. Preparation of the compound where R', R" and R''' are each methyl, R_{x2}, R_{y1}, R_{y2}, R_{y3}, R_{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R_{x1} is 6-aminohexyl

25 The desired subtitled compound was prepared substantially in accordance with the procedure detailed in Example 4A, using the compound from Example 5A, a catalytic amount (10 mol percent) of 10% palladium-on-carbon, and two drops of glacial acetic acid in a 1:1 mixture of methanol and water, under 1 atmosphere of hydrogen (gas).

Yield: 102 mg.

MS(FAB): 1361.7 (M+Na).

30

Example 6

35 Preparation of the compound where R', R" and R''' are each methyl, R_{x2}, R_{y1}, R_{y2}, R_{y3}, R_{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R_{x1} is carboxymethyl

40 A solution containing 2.00 g (1.75 mmol) of the compound depicted in Table 2II, 2.668 g (35.08 mmol) of glycolic acid, and 66 mg (0.350 mmol) of p-toluenesulfonic acid in 40 ml of dioxane was allowed to react at room temperature. When the reaction was substantially complete,

as indicated by TLC, the reaction mixture was filtered and the resultant filtrate was applied to a reverse phase preparative HPLC column (eluent of 50% aqueous acetonitrile containing 0.1% trifluoroacetic acid; 80 ml/min.; 280 nm).
5 The fractions containing the desired compound were combined and concentrated *in vacuo* to provide 0.770 g of an off-white solid which was determined to be 86.5% pure using HPLC (C18; eluent of 55% aqueous acetonitrile containing 0.1% trifluoroacetic acid, 2 ml/min.; 280 nm;
10 $R_T = 4.13$ min.).
Yield: 37%.
MS(FAB): 1162.7 (M-2H₂O)

Example 7

15 Preparation of the compound where R', R" and R''' are each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R^{x1} is carboxymethyl, sodium salt
20 To a suspension of 0.3 g (0.25 mmol) of the compound of Example 6 in 5 ml of water, was added 0.25 ml of 1N sodium hydroxide (0.25 mmol). The resultant reaction mixture was slowly heated until the solid went into solution. The resultant solution was lyophilized to
25 provide 236 mg of the desired titled compound.
MS(FAB): 1221.7 (M⁺)

Example 8

30 Preparation of the compound where R', R" and R''' are each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R^{x1} is methyl
To a solution of 400 mg of the compound depicted in Table 2II in 30 ml of methanol, was added approximately
35 1 ml of 1N hydrochloric acid. When the reaction was substantially complete, as determined by HPLC (eluent of 50% aqueous acetonitrile; 2 ml/min.; 280 nm), the reaction mixture was applied to a preparative HPLC column (eluent of

50% aqueous acetonitrile, 90 ml/min.; 280 nm). The fractions containing the desired compound were combined and concentrated *in vacuo* to provide 223.7 mg of the titled compound which was determined to be 98.7% pure using HPLC (eluent of 50% aqueous acetonitrile; 2 ml/min.; 280 nm; R_T = 8.55 min.).

MS (FAB) for $C_{59}H_{75}N_7O_{17}Na$

Calcd: 1176.5117 (M+Na);

Found: 1176.5140.

10

Example 9

Preparation of the compound where R', R'' and R''' are each methyl, R_{X2} , R_{Y1} , R_{Y2} , R_{Y3} , R_{Y4} and R_0 are each hydroxy, R_2 is the acyl group depicted in Table 2II and R_{X1} is 2-aminoethyl, hydrochloride salt

A stream of hydrochloric acid (gas) was briefly passed over the surface of a solution containing 1.0 g (0.88 mmol) of the compound depicted in Table 2II and 1.71 g (88.0 mmol) of ethanolamine hydrochloride in 15 ml of dimethylsulfoxide. The resultant reaction mixture was allowed to react for approximately ninety six hours. When the reaction was substantially complete, as indicated by HPLC (C18; eluent of 50% aqueous acetonitrile containing 0.5% monobasic ammonium phosphate; 2 ml/min, 280 nm), the desired compound was isolated using preparative HPLC (C18; eluent of 45% aqueous acetonitrile containing 0.1% trifluoroacetic acid; 90 ml/min). The fractions containing the desired compound were combined and concentrated *in vacuo* to provide 490 mg which was determined to be 96% pure using HPLC (C18; eluent of 50% aqueous acetonitrile containing 0.5% monobasic ammonium phosphate; 2 ml/min.; R_T = 2.96 min.).

Yield: 43%.

MS (FAB): 1183 (M⁺).

Example 10

Preparation of the compound where R', R" and R''' are each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R^{x1} is ethylphosphonic acid, dimethylester

To a mixture containing 1 g (0.88 mmol) of the compound depicted in Table 2II and 11 ml (88 mmol) of dimethyl-2-hydroxyethylphosphonate in 10 ml of dioxane, was added 17 mg (0.088 mmol) of p-toluenesulfonic acid. The resultant reaction mixture was allowed to react for approximately twenty three hours. When the reaction was substantially complete, as indicated by HPLC (C18; eluent of 50% aqueous acetonitrile; 2 ml/min, 280 nm), the desired compound was isolated using preparative reverse phase HPLC (C18; gradient eluent of 45-48% aqueous acetonitrile; 90 ml/min). The fractions containing the desired compound were combined and concentrated in vacuo to provide 753 mg which was determined to be 94% pure using HPLC (C18; eluent of 50% aqueous acetonitrile; 2 ml/min, 280 nm; R_T = 7.2 min.).

Yield: 67%.

MS (FAB) for C₆₂H₈₂N₇O₂₀PNa

Calcd: 1298.5250 (M+Na);

Found: 1298.5281.

Example 11

Preparation of the compound where R', R" and R''' are each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II, and R^{x1} is ethylphosphonic acid, monomethylester

A solution of 22.5 mg (0.936 mmol) of lithium hydroxide in 2 ml of water was added to a slurry of 200 mg (0.156 mmol) of the titled compound of Example 10 in 5 ml of dioxane. The resultant reaction mixture was allowed to react for approximately 6.5 hours. When the reaction was substantially complete, as indicated by HPLC (C18; eluent of 50% aqueous acetonitrile containing 0.5% monobasic

ammonium phosphate; 2 ml/min, 280 nm), the desired compound was isolated using preparative HPLC (C18; eluent of 40% aqueous acetonitrile, 90 ml/min., 280 nm). The fractions containing the desired compound were combined and concentrated in vacuo to provide 43 mg which was determined to be 98% pure using HPLC (C18; eluent of 45% aqueous acetonitrile containing 0.5% monobasic ammonium phosphate; 2 ml/min, 280 nm; R_T = 4.47 min.).

Yield: 22%.

MS(FAB) for $C_{61}H_{80}N_7O_{20}PLi$

Calcd: 1268.5356 (M+Li);

Found: 1268.5403.

Example 12

Preparation of the compound where R', R" and R''' are each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II, and R^{x1} is 2-(2-ethoxyethoxy)ethyl

A solution containing 1.00 mg (0.877 mmol) of the compound depicted in Table 2II, 11.780 ml (87.690 mmol) of 2-(2-ethoxyethoxy)ethanol, and 0.34 g (0.175 mmol) of p-toluenesulfonic acid in 20 ml of dioxane was allowed to react for approximately thirty six hours. When the reaction was substantially complete, as indicated by TLC, 6.48 g (0.0876 mmol) of sodium bicarbonate was added to the reaction and the resultant mixture was concentrated in vacuo to provide 0.160 g of a white solid which was determined to be 99.6% pure using HPLC (C18; eluent of 65% aqueous acetonitrile containing 0.5% monobasic ammonium phosphate; 2 ml/min, 280 nm; R_T = 3.58 min.).

Yield: 14%.

MS(FAB) for $C_{64}H_{85}N_7O_{19}Li$:

Calcd: 1262.6060 (M+Li);

Found: 1262.6074

Example 13A. 2-(N-methyl-N-butylamino)ethanol hydrochloride

Hydrochloric acid (gas) was bubbled through a solution of 10.0 g (0.0762 mmol) of 2-(N-methyl-N-butylamino)ethanol in diethyl ether. The resultant solution was concentrated *in vacuo* to provide a gold oil.

B. Preparation of the compound where R', R'' and R''' are each methyl, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R^{x1} is 2-(N-methyl-N-butylamino)ethyl

To a solution of the oil isolated in Example 13A in 100 ml of dimethylsulfoxide, was added 1.00 g (0.877 mmol) of the compound depicted in Table 2II. A stream of hydrochloric acid (gas) was briefly passed over the surface of the solution and then the resultant reaction mixture was allowed to react for approximately one week. When the reaction was substantially complete, as indicated by HPLC (eluent of 50% aqueous acetonitrile containing 0.1% trifluoroacetic acid), the reaction mixture was filtered. The resultant filtrate was applied to a preparatory HPLC column (eluent of 50% aqueous acetonitrile containing 0.1% trifluoroacetic acid; 80 ml/min.; 280 nm). The fractions containing the desired compound were combined and concentrated *in vacuo* to provide 40 mg of a white fluffy solid which was determined to be 85.6% pure using HPLC (C18; eluent of 50% aqueous acetonitrile containing 0.1% trifluoroacetic acid; 2 ml/min.; 280 nm; R_T = 4.75 min.). Yield: 3.7%.

MS(FAB) for C₅₆H₈₉N₈O₁₇

Calcd: 1253.6346 (M);

Found: 1253.6393.

Example 14

Preparation of the compound where R', R" and R''' are each methyl, Rx2, Ry1, Ry2, Ry3, Ry4 and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and Rx1 is 2-(N,N-dimethylamino)ethyl

The titled compound was prepared substantially in accordance with the procedures detailed in Examples 13A and 13B, using 17.63 ml (175.39 mmol) of 2-(N,N-dimethylamino)ethanol, 2.00 g (1.75 mmol) of the compound depicted in Table 2II, and hydrochloric acid (gas) to provide 0.559 g of a white fluffy solid which was determined to be 99.9% pure using HPLC (C18; eluent of 50% aqueous acetonitrile containing 0.1% trifluoroacetic acid; 2 ml/min.; 280 nm; R_T = 5.39 min.).

Yield: 26%.

MS(FAB) for C₆₂H₈₃N₈O₁₇

Calcd: 1211.5876 (M);

Found: 1211.5883.

Example 15

Preparation of the compound where R', R" and R''' are each methyl, Rx2, Ry1, Ry2, Ry3, Ry4 and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and Rx1 is 2-pyrrolidin-1-ylethyl

The titled compound was prepared substantially in accordance with the procedures detailed in Examples 13A and 13B, using 20.51 ml (175.39 mmol) of 1-(2-hydroxyethyl)pyrrolidine, 2.00 g (1.75 mmol) of the compound depicted in Table 2II, and hydrochloric acid (gas) to provide 363 mg of a white fluffy solid which was determined to be 96.8% pure using HPLC (C18; eluent of 55% aqueous acetonitrile containing 0.1% trifluoroacetic acid; 2 ml/min.; 280 nm; R_T = 3.84 min.).

Yield: 17%.

MS(FAB) for C₆₄H₈₅N₈O₁₇

Calcd: 1237.6033 (M);

Found: 1237.5991.

Example 16

Preparation of the compound where R', R" and R''' are each methyl, Rx2, Rv1, Rv2, Rv3, Rv4 and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and Rx1 is 2-(N-methyl-N-ethylamino)ethyl

The titled compound was prepared substantially in accordance with the procedures detailed in Examples 13A and 13B, using 20 ml (175.39 mmol) of N,N-dimethylethanolamine, 2.00 g (1.75 mmol) of the compound depicted in Table 2II, and hydrochloric acid (gas) to provide 0.975 g of a white fluffy solid which was determined to be 97.3% pure using HPLC (C18; eluent of 50% aqueous acetonitrile containing 0.1% trifluoroacetic acid; 2 ml/min.; 280 nm; R_T = 4.8 min.).

Yield: 46%.

MS(FAB) for C₆₃H₈₅N₈O₁₇

Calcd: 1225.6033 (M);

Found: 1225.5995.

Example 17

Preparation of the compound where R', R" and R''' are each methyl, Rx2, Rv1, Rv2, Rv3, Rv4 and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and Rx1 is benzyl

The desired compound was prepared substantially in accordance with the procedure detailed in Example 4A, using 750 mg (0.658 mmol) of the compound depicted in Table 2II, 3.404 ml (32.89 mmol) of benzylic alcohol, and a catalytic amount (approximately 10 mol percent) of p-toluenesulfonic acid in 50 ml of dioxane.

MS(FAB) for C₆₅H₈₀N₇O₁₇

Calcd: 1230.5611 (M⁺);

Found: 1230.5650.

Example 18

Preparation of the compound where R', R'' and R''' are each methyl, R_{X2}, R_{Y1}, R_{Y2}, R_{Y3}, R_{Y4} and R₀ are each hydroxy, R₂ is the acyl group depicted in Table 2II and R_{X1} is 2-(trimethylsilyl)ethyl

To a solution of 2.5 g (1.8 mmol) of the compound of Table 2II and 25 ml (175 mmol) of 2-(trimethylsilyl)ethanol in 50 ml of dioxane at room temperature, was added a catalytic amount of p-toluenesulfonic acid. The resultant reaction mixture was allowed to react at room temperature for approximately seven hours. When the reaction was substantially complete, as indicated by HPLC, the reaction was quenched with solid sodium bicarbonate and filtered. The desired titled compound was isolated from the filtrate using reverse phase HPLC (50% acetonitrile/50% water; 50 ml/min.; 280 nm). MS(FAB): 1262.7 (M+Na)

The compounds of formula I exhibit antifungal and antiparasitic activity. For example, the compounds of formula I inhibit the growth of various infectious fungi including Candida spp. such as *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. glabrata*, or *C. tropicalis*, *C. lusitaniae*; *Torulopus spp.* such as *T. glabrata*; *Aspergillus spp.* such as *A. fumigatus*; *Histoplasma spp.* such as *H. capsulatum*; *Cryptococcus spp.* such as *C. neoformans*; *Blastomyces spp.* such as *B. dermatitidis*; *Fusarium spp.*, *Trichophyton spp.*, *Pseudallescheria boydii*, *Coccidioides immitis*, *Sporothrix schenckii* and the like.

Antifungal activity of a test compound is determined *in vitro* by obtaining the minimum inhibitory concentration (MIC) of the compound using a standard agar dilution test or a disc-diffusion test. The compound is then tested *in vivo* (in mice) to determine the effective dose of the test compound for controlling a systemic fungal infection.

Accordingly, the following compounds were tested for antifungal activity against *C. albicans*:

Table 3

5 Minimal inhibitory concentration against *C. albicans*

	<u>Example No.</u>	<u>MIC (μg/ml)</u>
	2B	0.039
	3B	0.0098
10	4B	0.312
	5B	0.312
	6	0.078
	7	0.039
	8	0.005
15	9	0.020
	10	0.020
	11	0.039
	12	0.156
	13	0.625
20	14	0.156
	15	0.312
	16	0.156
	17	N.T.
	18	0.25

25

N.T. not tested.

In addition, the effective dose of the following compounds for controlling a systemic fungal infection (*C. albicans*) was tested *in vivo* (mice).

30

Table 4
ED₅₀ (mouse)

	<u>Example No.</u>	<u>ED₅₀ (mg/kg)</u>
5	2B	
	3B	
	4B	
	5B	
	6	>2.5
10	7	1.38
	8	0.99
	9	0.312
	10	1.25
	11	1.13
15	12	>2.5
	13	0.47
	14	0.312
	15	0.34
	16	0.34
20	17	N.T.
	18	>2.5

N.T. not tested.

The compounds of the invention also inhibit the growth of certain organisms primarily responsible for opportunistic infections in immunosuppressed individuals. For example the compounds of the invention inhibit the growth of *Pneumocystis carinii* the causative organism of pneumocystis pneumonia (PCP) in AIDS and other immunocompromised patients. Other protozoans that are inhibited by compounds of formula I include *Plasmodium* spp., *Leishmania* spp., *Trypanosoma* spp., *Cryptosporidium* spp., *Isospora* spp., *Cyclospora* spp., *Trichomonas* spp., *Microsporidiosis* spp. and the like.

The compounds of formula I are active *in vitro* and *in vivo* and are useful in combating either systemic fungal infections or fungal skin infections. Accordingly,

the present invention provides a method of inhibiting fungal activity comprising contacting a compound of formula I, or a pharmaceutically acceptable salt thereof, with a fungus. A preferred method includes inhibiting *Candida albicans* or *Aspergillus fumigatis* activity. The present invention further provides a method of treating a fungal infection which comprises administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, to a host in need of such treatment. A preferred method includes treating a *Candida albicans* or *Aspergillus fumigatis* infection.

With respect to antifungal activity, the term "effective amount," means an amount of a compound of the present invention which is capable of inhibiting fungal activity. The dose administered will vary depending on such factors as the nature and severity of the infection, the age and general health of the host and the tolerance of the host to the antifungal agent. The particular dose regimen likewise may vary according to such factors and may be given in a single daily dose or in multiple doses during the day. The regimen may last from about 2-3 days to about 2-3 weeks or longer. A typical daily dose (administered in single or divided doses) will contain a dosage level of from about 0.01 mg/kg to about 100 mg/kg of body weight of an active compound of this invention. Preferred daily doses generally will be from about 0.1 mg/kg to about 60 mg/kg and ideally from about 2.5 mg/kg to about 40 mg/kg.

The present invention also provides pharmaceutical formulations useful for administering the antifungal compounds of the invention. Accordingly, the present invention also provides a pharmaceutical formulation comprising one or more pharmaceutically acceptable carriers, diluents or excipients and a compound of claim 1. The active ingredient in such formulations comprises from 0.1% to 99.9% by weight of the formulation, more generally from about 10% to about 30% by weight. By "pharmaceutically acceptable" it is meant that the carrier,

diluent or excipient is compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

5 A compound of formula I may be administered parenterally, for example using intramuscular, subcutaneous, or intra-peritoneal injection, nasal, or oral means. In addition to these methods of administration, a compound of formula I may be applied topically for skin infections.

10 For parenteral administration the formulation comprises a compound of formula I and a physiologically acceptable diluent such as deionized water, physiological saline, 5% dextrose and other commonly used diluents. The formulation may contain a solubilizing agent such as a
15 polyethylene glycol or polypropylene glycol or other known solubilizing agent. Such formulations may be made up in sterile vials containing the antifungal and excipient in a dry powder or lyophilized powder form. Prior to use, a physiologically acceptable diluent is added and the
20 solution withdrawn via syringe for administration to the patient.

The present pharmaceutical formulations are prepared by known procedures using known and readily available ingredients. In making the compositions of the
25 present invention, the active ingredient will generally be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid
30 or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, (as a solid or in a liquid
35 medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin

capsules, suppositories, sterile injectable solutions, sterile packaged powders and the like.

For oral administration, the antifungal compound is filled into gelatin capsules or formed into tablets.

5 Such tablets may also contain a binding agent, a dispersant or other suitable excipients suitable for preparing a proper size tablet for the dosage and particular antifungal compound of the formula I. For pediatric or geriatric use the antifungal compound may be formulated into a flavored
10 liquid suspension, solution or emulsion. A preferred oral formulation is linoleic acid, cremophor RH-60 and water and preferably in the amount (by volume) of 8% linoleic acid, 5% cremophor RH-60, 87% sterile water and a compound of formula I in an amount of from about 2.5 to about 40 mg/ml.

15 For topical use the antifungal compound may be formulated with a dry powder for application to the skin surface or it may be formulated in a liquid formulation comprising a solubilizing aqueous liquid or non-aqueous liquid, e.g., an alcohol or glycol.

20 The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way. The term "active ingredient" means a compound according to formula I or a pharmaceutically acceptable salt thereof.

25

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

30

	Quantity <u>(mg/capsule)</u>
Active ingredient	250
Starch, dried	200
35 Magnesium stearate	<u>10</u>
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

5		Quantity (mg/capsule)
	Active ingredient	250
	Cellulose, microcrystalline	400
10	Silicon dioxide, fumed	10
	Stearic acid	<u>5</u>
	Total	665 mg

15 The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

An aerosol solution is prepared containing the following components:

20		<u>Weight</u>
	Active ingredient	0.25
	Methanol	25.75
25	Propellant 22	
	(Chlorodifluoromethane)	<u>74.00</u>
	Total	100.00

30 The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to
-30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve
35 units are then fitted to the container.

Formulation 4

Tablets, each containing 60 mg of active ingredient, are made as follows:

5	Active ingredient	60 mg
	Starch	45 mg
	Microcrystalline cellulose	35 mg
	Polyvinylpyrrolidone	
	(as 10% solution in water)	4 mg
10	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	<u>1 mg</u>
	Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules, each containing 80 mg of active ingredient, are made as follows:

30	Active ingredient	80 mg
	Starch	59 mg
	Microcrystalline cellulose	59 mg
	Magnesium stearate	<u>2 mg</u>
	Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

5

Formulation 6

Suppositories, each containing 225 mg of active ingredient, are made as follows:

10	Active ingredient	225 mg
	Saturated fatty acid glycerides	<u>2,000 mg</u>
	Total	2,225 mg

15 The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

20

Formulation 7

Suspensions, each containing 50 mg of active ingredient per 5 ml dose, are made as follows:

	Active ingredient	50 mg
25	Sodium carboxymethyl cellulose	50 mg
	Syrup	1.25 ml
	Benzoic acid solution	0.10 ml
	Flavor	q.v.
	Color	q.v.
30	Purified water to total	5 ml

35 The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

An intravenous formulation may be prepared as follows:

5

Active ingredient	100 mg
Isotonic saline	1,000 ml

10

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

15

20

25

The present invention further provides a method for treating or preventing the onset of Pneumocystis pneumonia in a host susceptible to Pneumocystis pneumonia which comprises administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, to a host in need of such treatment. The compounds of formula I can be used prophylactically to prevent the onset of the infection which is caused by the organism Pneumocystis carinii, or alternatively they can be used to treat a host that has been infected with P. carinii. A compound of formula I may be administered parenterally, for example using intramuscular, intravenous or intra-peritoneal injection, orally or by inhaling directly into the airways of the lungs. A preferred mode of administration is inhalation of an aerosol spray formulation of a compound of formula I.

30

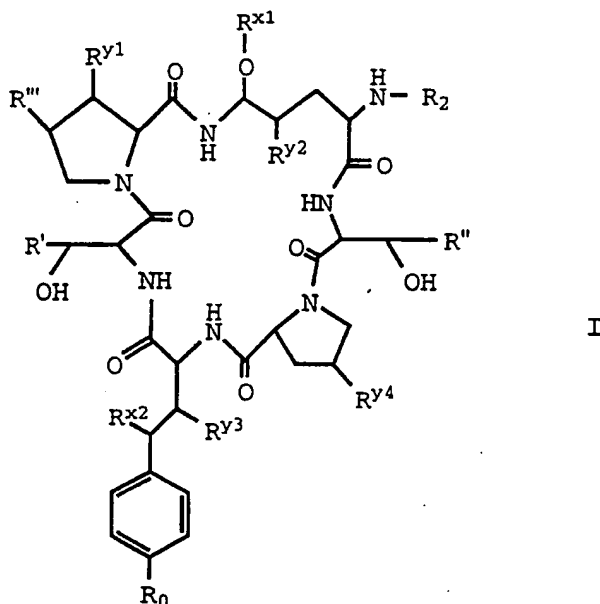
35

With respect to antiparasitic activity, the term "effective amount," means an amount of a compound of the present invention which is capable of inhibiting parasitic activity. An effective amount of the compound of formula I is from about 3 mg/kg of patient body weight to about 100 mg/kg. The amount administered may be in a single daily dose or multiple doses of, for example, two, three or four times daily throughout the treatment regimen. The amount of the individual doses, the route of delivery, the frequency of dosing and the term of therapy will vary

according to such factors as the intensity and extent of infection, the age and general health of the patient, the response of the patient to therapy and how well the patient tolerates the drug. It is known that Pneumocystis pneumonia infections in AIDS patients are highly refractory owing to the nature of the infection. For example, in severe, advanced infections the lumenal surface of the air passages becomes clogged with infectious matter and extensive parasite development occurs in lung tissue. A patient with an advanced infection will accordingly require higher doses for longer periods of time. In contrast, immune deficient patients who are not severely infected and who are susceptible to Pneumocystis pneumonia can be treated with lower and less frequent prophylactic doses.

CLAIMS

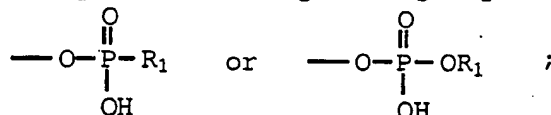
1. A compound of formula I:



wherein:

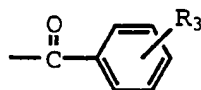
- R' is hydrogen, methyl or $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$;
- R'' and R''' are independently hydrogen or methyl;
- Rx1 is $\text{C}_1\text{-C}_6$ alkyl, benzyl, $-(\text{CH}_2)_2\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CHOHCH}_2\text{OH}$, $-(\text{CH}_2)_a\text{COOH}$, $-(\text{CH}_2)_b\text{NR}^{\text{z1}}\text{R}^{\text{z2}}$, $-(\text{CH}_2)_c\text{POR}^{\text{z3}}\text{R}^{\text{z4}}$ or $-[(\text{CH}_2)_2\text{O}]_d-(\text{C}_1\text{-C}_6)\text{alkyl}$;
- a, b and c are independently 1, 2, 3, 4, 5 or 6;
- Rz1 and Rz2 are independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl, or Rz1 and Rz2 combine to form $-\text{CH}_2(\text{CH}_2)_e\text{CH}_2-$;
- Rz3 and Rz4 are independently hydroxy, or $\text{C}_1\text{-C}_6$ alkoxy;
- d is 1 or 2;
- e is 1, 2 or 3;
- Rx2, Ry1, Ry2, Ry3 and Ry4 are independently hydroxy or hydrogen;

R₀ is hydroxy, -OP(O)(OH)₂ or a group of the formulae:



R₁ is C₁-C₆ alkyl, phenyl, p-halo-phenyl, p-nitrophenyl, benzyl, p-halo-benzyl or p-nitro-benzyl;

I) R₂ is a group of the formula

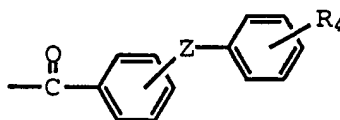


where:

- A) R₃ is C₁-C₁₂ alkyl, C₁-C₆ alkoxy or quinolyl;
- B) R₃ is -O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl);
m and n are independently 2, 3 or 4;
p is 0 or 1; or
- C) R₃ is -Y-(C₁-C₁₂ alkyl);
Y is -C≡C- or -CH=CH-; or
- D) R₃ is -O-(CH₂)_q-G;
q is 2, 3 or 4;
G is C₇-C₁₀ bicycloalkyl or C₇-C₁₄

tricycloalkyl; or

II) R₂ is a group of the formula



where:

Z is -O-, -C≡C-, -CH=CH-, -CH₂-CH₂-, -CH₂-, or a bond;

- A) R₄ is hydrogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ alkynyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy, C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₃-C₁₂ cycloalkoxy, naphthyl, pyridyl, thienyl, benzothienyl, quinolyl or phenyl; or

B) R_4 is phenyl substituted by amino, C_1 - C_{12} alkylthio, halo, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, C_1 - C_{12} substituted alkyl, C_2 - C_{12} substituted alkenyl, C_2 - C_{12} substituted alkynyl, C_1 - C_{12} alkoxy, trifluoromethyl, phenyl, substituted phenyl, or phenyl substituted with a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m , n and p are as defined above; or

C) R_4 is C_1 - C_{12} alkoxy substituted with halo, C_3 - C_{12} cycloalkyl, C_7 - C_{10} bicycloalkyl, C_7 - C_{14} tricycloalkyl, C_1 - C_6 alkoxy, C_2 - C_{12} alkynyl, amino, C_1 - C_4 alkylamino, di(C_1 - C_4 alkyl)amino, formamido, C_2 - C_{12} alkanoylamino, or phenyl substituted with a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m , n and p are as defined above; or

D) R_4 is $-O-(CH_2)_r-W-R_5$;
 r is 2, 3 or 4;
 W is pyrrolidino, piperidino or piperazino;
 R_5 is hydrogen, C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, benzyl or C_3 - C_{12} cycloalkylmethyl; or

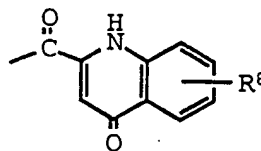
E) R_4 is $-Y^1-R_6$;
 Y^1 is $-C\equiv C-$ or $-CH=CH-$;
 R_6 is C_3 - C_{12} cycloalkyl, C_7 - C_{10} bicycloalkyl, C_7 - C_{14} tricycloalkyl, C_3 - C_{12} cycloalkenyl, naphthyl, benzothiazolyl, thienyl, indanyl, fluorenyl, or phenyl substituted with C_1 - C_{12} alkylthio, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, halo(C_1 - C_6 alkoxy) or a group of the formula $-O-(CH_2)_r-W-R_5$ where r , W and R_5 are as defined above; or

R_6 is phenyl substituted with a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m , n and p are as defined above; or

F) R_4 is C_1 - C_{12} alkoxy substituted with a group of the formula $-NHC(O)R_7$;

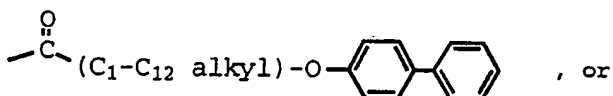
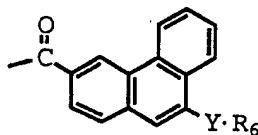
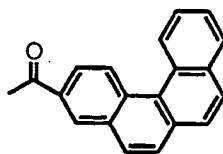
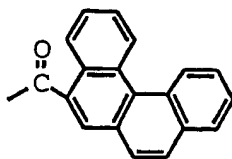
R_7 is C_1 - C_6 alkoxy, or phenyl(C_1 - C_6 alkoxy); or

III) R_2 is a group of the formula

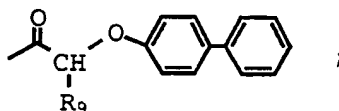


where R^8 is C_1 - C_{12} alkoxy or a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m , n and p are as defined above; or

IV) R_2 is a group of the formula



, or



where:

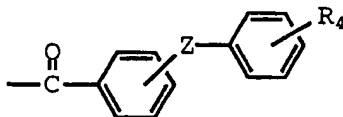
Y and R_6 are as defined above;

R_9 is phenyl, C_1 - C_{12} alkyl, or C_1 - C_{12} alkoxy; or

V) R_2 is naphthoyl substituted with R_4 where R_4 is as defined above;

with the provisos that:

i) when R' is $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$; and $\text{R}^{\text{x}1}$ is methyl or benzyl; then R_2 is not a group of the formula



where:

Z is a bond;

A) R_4 is C_1 - C_{12} alkoxy; or

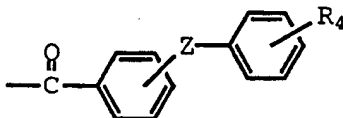
B) R_4 is phenyl substituted by C_1 - C_{12} alkoxy; or

C) R_4 is C_1 - C_{12} alkoxy substituted with C_1 - C_4 alkylamino, di(C_1 - C_4 alkyl)amino; or

D) R_4 is $-\text{O}-(\text{CH}_2)_r-\text{W}-\text{R}_5$;

W is piperidino or piperazino;

ii) when $\text{R}^{\text{x}1}$ is $-(\text{CH}_2)_b\text{NR}^{\text{z}1}\text{R}^{\text{z}2}$; then R_2 is not a group of the formula



where:

Z is a bond;

A) R_4 is C_1 - C_{12} alkoxy; or

B) R_4 is phenyl substituted by C_1 - C_{12} alkoxy; or

C) R_4 is C_1 - C_{12} alkoxy substituted with C_1 - C_4 alkylamino, di(C_1 - C_4 alkyl)amino; or

D) R_4 is $-\text{O}-(\text{CH}_2)_r-\text{W}-\text{R}_5$;

W is piperidino or piperazino;

or a pharmaceutically acceptable salt thereof.

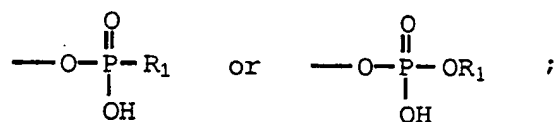
2. A compound according to claim 1 where:

R' , R'' and R''' are each methyl;

$\text{R}^{\text{y}1}$, $\text{R}^{\text{y}2}$, $\text{R}^{\text{y}3}$ and $\text{R}^{\text{y}4}$ are each hydroxy;

$\text{R}^{\text{x}2}$ is hydroxy;

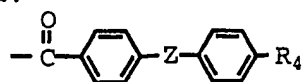
R₀ is hydroxy or a group of the formulae:



R₁ is methyl;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2 where R₂ is a group of the formula:



where Z is $\text{---C}\equiv\text{C---}$ or a bond;

A) R₄ is hydrogen, C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ alkynyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy, C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₃-C₁₂ cycloalkoxy, naphthyl, pyridyl, thienyl, benzothienyl, quinolyl or phenyl; or

B) R₄ is phenyl substituted by amino, C₁-C₁₂ alkylthio, halo, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ substituted alkyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, phenyl, substituted phenyl, or a group of the formula $\text{---O---(CH}_2\text{)}_m\text{---[O---(CH}_2\text{)}_n\text{]}_p\text{---O---(C}_1\text{---C}_{12}\text{ alkyl)}$ where m, n and p are as defined above; or

C) R₄ is C₁-C₁₂ alkoxy substituted with halo, C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₁-C₆ alkoxy, C₂-C₁₂ alkynyl, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, formamido, C₂-C₁₂ alkanoylamino, or phenyl substituted with a group of the formula $\text{---O---(CH}_2\text{)}_m\text{---[O---(CH}_2\text{)}_n\text{]}_p\text{---O---(C}_1\text{---C}_{12}\text{ alkyl)}$ where m, n and p are as defined above; or

D) R_4 is $-O-(CH_2)_r-W-R_5$;
 r is 2, 3 or 4;
 W is pyrrolidino, piperidino or piperazino;
 R_5 is hydrogen, C_1 - C_{12} alkyl, C_3 - C_{12} cycloalkyl, benzyl or C_3 - C_{12} cycloalkylmethyl; or

E) R_4 is $-Y^1-R_6$;
 Y^1 is $-C\equiv C-$ or $-CH=CH-$;
 R_6 is C_3 - C_{12} cycloalkyl, C_7 - C_{10} bicycloalkyl, C_7 - C_{14} tricycloalkyl, C_3 - C_{12} cycloalkenyl, naphthyl, benzothiazolyl, thienyl, indanyl, fluorenyl, or phenyl substituted with C_1 - C_{12} alkylthio, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, halo(C_1 - C_6 alkoxy) or a group of the formula $-O-(CH_2)_r-W-R_5$ where r , W and R_5 are as defined above; or

R_6 is phenyl substituted with a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m , n and p are as defined above; or

F) R_4 is C_1 - C_{12} alkoxy substituted with a group of the formula $-NHC(O)R_7$;

R_7 is C_1 - C_6 alkoxy, or phenyl(C_1 - C_6 alkoxy); or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 3 where:

R^{x1} is C_1 - C_4 alkyl, benzyl, $-CH_2CHOHCH_2OH$, $-CH_2COOH$, $-(CH_2)_bNR^{z1}R^{z2}$ or $-(CH_2)_2POR^{z3}R^{z4}$;

b is 2, 3, 4, 5 or 6;

R^{z1} and R^{z2} are independently hydrogen or C_1 - C_4 alkyl; and

R^{z3} and R^{z4} are independently hydrogen or methoxy;

or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 4 where:

R^{x1} is $-CH_2CHOHCH_2OH$, $-CH_2COOH$ or $-(CH_2)_2POR^{z3}R^{z4}$;

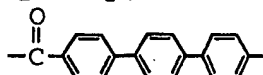
and

R^{z3} and R^{z4} are independently hydrogen or methoxy;

or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 4 where:

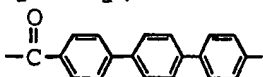
R₀ is hydroxy;

R₂ is ; and

R_{x1} is $-\text{CH}_2\text{CHOHCH}_2\text{OH}$;

or a compound where:

R₀ is hydroxy;

R₂ is ; and

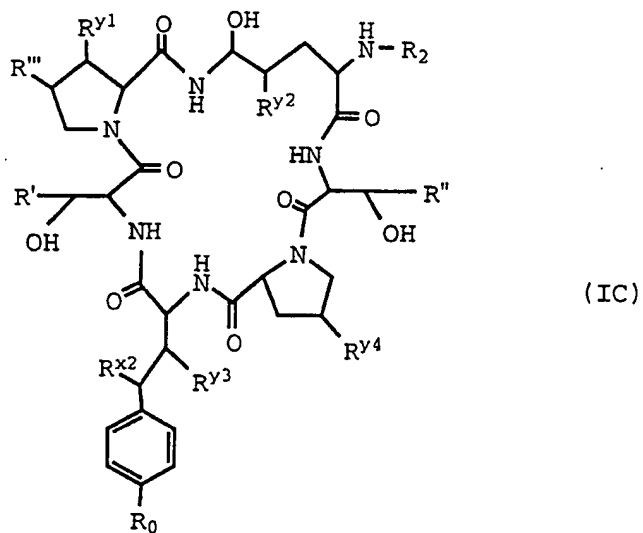
R_{x1} is methyl;

or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical formulation comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 6, associated with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

8. A compound of formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 6, for use as a pharmaceutical.

9. A process for preparing a compound of formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 6, comprising etherifying a compound of formula IC:



or a pharmaceutically acceptable salt thereof;
where:

R', R'', R''', R_{x2}, R_{y1}, R_{y2}, R_{y3}, R_{y4}, R₀ and R₂ are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/07244

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07K 7/56, 7/64

US CL :514/9, 11; 530/317

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/9, 11; 530/317

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,166,135 (SCHMATZ) 24 November 1992, see abstract and columns 2-4.	1-9

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Further documents are listed in the continuation of Box C.

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See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

12 AUGUST 1996

Date of mailing of the international search report

23 AUG 1996

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